Oxford Vascular Study: Design and initial results of a population-based study of the incidence and outcome of all acute vascular events

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To

Alison, Emma,

Matthew and Rachel

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Declaration

I declare that this thesis is of my own composition, and the research contained herein is my own original work. No portion of this work has been submitted in support of an application for any other degree.

Andrew John Coull

1st September 2004

Acknowledgements

I am indebted to many people who helped and encouraged me to perform this research. Above all, I thank the many patients and their relatives whose co-operation allowed this work to be possible. I am grateful to the General Practitioners from our study practices and their administrative staff who were enormously helpful in identifying patients. I thank the many staff in both the John Radcliffe Hospital and the Radcliffe Infirmary who gave me their full co-operation in setting up the Oxford Vascular Study. Individually, I am extremely grateful to Louise Silver, Research Nurse who always managed to encourage throughout. I thank Patricia Edwards for her tireless administrative support. I acknowledge and thank Linda Bull, Research Nurse and Dr Matthew Giles for their help and support. I also thank Sally Howard and Sergei Gutnikov for their statistical advice. I am particularly indebted to Dr Peter Rothwell, Director of the Stroke Prevention Research Unit for his continual support and enthusiasm for the study.

Abstract

Background

Arterial diseases are the leading cause of death and disability in the developed world, and are rapidly increasing in importance in the developing world. The incidence, case-fatality, and longer-term sequelae of transient ischaemic attack (TIA), stroke, acute coronary syndromes (ACS) and peripheral vascular events (PVE) have never been measured in the same population at the same time, and the time-trends in incidence and case-fatality are uncertain.

Aims

- To develop the Oxford Vascular (OXVASC) Study protocol and ensure case ascertainment was reliable and complete.
- To examine the effects of case definition and quality of methods of ascertainment on stroke incidence rates.
- To examine the effect of definition on the risk of recurrent stroke
- To determine the early risk of stroke after a TIA or minor stroke.
- To compare the incidence and estimate time trends in stroke incidence by comparison with the Oxfordshire Community Stroke Project (OCSP).
- To measure and compare the incidence and burden of stroke, ACS and PVE.

Methods

OXVASC is a population-based study of all acute vascular events (TIA, stroke, ACS and PVE) and elective surgical and endovascular interventions for subacute or chronic vascular disease in Oxfordshire. The pilot study covered a population of 90,542 in 9 general practices. Multiple overlapping sources of ascertainment were used to identify cases from hospitals and the community. Retrospective data were obtained for vascular deaths.

Summary of main findings

- The methods used in OXVASC achieved near-complete ascertainment. However, our analyses suggested that differences in case definition and ascertainment strategies between studies could each lead to differences in measured stroke incidence of up to 20% (Chapter 4, 5).

- The early risk of recurrence can vary two-fold depending on which definition is used. The 90 day risks (95%CI) of recurrent stroke with a 24 hour definition of recurrence were 18.3% (10.8-25.8) in OXVASC and 14.5% (11.5-17.5) in OCSP. The equivalent risks using a 28 day definition of recurrence were 5.9% (1.0-10.9) in OXVASC and 4.8% (2.8-6.7) in OCSP. Recurrences occurring after 24 hours should be used as the standard to avoid underestimation and to allow valid comparison between studies (Chapter 6).

- In OXVASC, the risks of stroke at 7 days after a TIA and minor stroke were 8.0% (95%CI=2.3–13.7) and 11.5% (95%CI=4.8-21.2) respectively. This is much higher than commonly quoted (Chapter 7).

- Recurrent stroke risk varies significantly between aetiological (TOAST) subtypes ($p<0.001$). Strokes due to large artery atherosclerosis had the highest odds of recurrence at 7 days (OR=3.3, 95%CI=1.5-7.0). They accounted for 37% of recurrences within 7 days highlighting the importance of urgent carotid imaging and endarterectomy (Chapter 8).

- The age-specific incidence of major stroke in Oxfordshire has fallen by 40% over the past 20 years in association with increased use of preventive treatments and major reductions in premorbid risk factors. Despite more complete case ascertainment than in OCSP, age-adjusted and sex-adjusted incidence of first-ever stroke fell by 29% (relative incidence 0·71, 95% CI 0·61–0·83, p=0·0002). Incidence

declined by more than 50% for primary intracerebral haemorrhage (0·47, 0·27–0·83, p=0·01) but was unchanged for subarachnoid haemorrhage (0·83, 0·44–1·57, p=0·57). Major reductions were recorded in mortality rates for incident stroke (0·63, 0·44–0·90, p=0·02) and in incidence of disabling or fatal stroke (0·60, 0·50–0·73, p<0·0001), but no change was seen in case-fatality due to incident stroke (17·2% vs 17·8%; age and sex adjusted relative risk 0·85, 95% CI 0·57–1·28, p=0·45). Comparison of premorbid risk factors revealed substantial reductions in the proportion of smokers, mean total cholesterol, and mean systolic and diastolic blood pressures and major increases in premorbid treatment with antiplatelet, lipid-lowering, and blood pressure lowering drugs (all p<0·0001).

- In OXVASC, non-fatal acute cerebrovascular events accounted for 46.7% of all incident acute vascular events. Resources for clinical services and research funding should reflect this (Chapter 10).

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Preface

I carried out the research described in this thesis between January 2002 and February 2004 as a Clinical Research Fellow and Honorary Registrar in Neurology in The Stroke Prevention Research Unit, Department of Clinical Neurology, University of Oxford, under the guidance of Dr Peter Rothwell. My secondary supervisor during this time was Professor Charles Warlow, Professor of Medical Neurology, Western General Hospital, Edinburgh. I developed the study protocol and designed and researched the content of the data collection forms. Between April 2002 and September 2003 I identified, enrolled and interviewed patients to be included in the study. This involved 'hot pursuit' daily weekday visits to the John Radcliffe Hospital to identify hospital inpatients with acute vascular events and each afternoon I ran a daily TIA and minor stroke clinic in the Radcliffe Infirmary. Over this 18 month period I personally saw or reviewed the medical notes of approximately 200 non-vascular events, 300 TIA and stroke, 250 ACS, 25 peripheral vascular events and 100 vascular intervention patients. I also performed the majority of 'cold pursuit' that involved weekly or monthly identification of patients using patient registers, angiography databases, electronic discharge coding data and Department of Public Health mortality files. I acknowledge the help of Louise Silver who saw other ACS and vascular intervention patients, Dr Matthew Giles, who joined the project in early 2003 and saw other TIA and stroke patients and Mr Jack Fairhead who joined the project in 2003 and saw other peripheral vascular event and vascular intervention patients. I also acknowledge the assistance of Mrs Linda Bull who gathered the majority of premorbid data from the collaborating GP practices. Between this period and also September 2003 to end of February 2004 I analysed, interpreted the data and wrote this thesis whilst also helping to collect and analyse the data for the two year incidence study. I acknowledge the statistical advice from Dr Peter Rothwell and Sally Howard in the Stroke Prevention Research Unit in the writing of this thesis.

Publications and presentations arising from this thesis

Publications

Coull AJ, Lovett JK, Rothwell PM, on behalf of the Oxford Vascular Study. Population-based study of the early risk of stroke after a TIA or minor stroke: justification for public education and a reorganisation of services. BMJ. 2004; 328:326-8.

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Presentations

A population-based study of the early risk of stroke after a TIA or minor stroke: justification for public education and a reorganisation of services. BASP. Cambridge January, 2004.

Invited Lecture

'News about Neuro.' West Berkshire Neurological Alliance. Stroke: Prevention, treatment and the community perspective. 28th March 2003.

List of abbreviations

ABPI	Ankle brachial pressure index
ACC	American College of Cardiology
ACS	Acute coronary syndrome
ASR	Age-sex register
AST	Aspartate transaminase
ASU	Acute Stroke Unit
CCU	Coronary Care Unit
CDCU	Cardiac Day Case Unit
CK	Creatinine kinase
CLI	Critical limb ischaemia
CT	Computer tomography
ECG	Electrocardiogram
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
FP	Family Practitioner
HRT	Hormone replacement therapy
JRH	John Radcliffe Hospital NHS Trust
LBBB	Left bundle branch block
LISI	Low income scheme index
MAU	Medical Admissions Unit
MI	Myocardial infarction
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NHS	National Health Service
NICI	Non ischaemic cardiac injury
NSTEMI	Non ST elevation myocardial infarction
OCP	Oral contraceptive pill
OCSP	Oxfordshire Community Stroke Project

ORH	Oxford Radcliffe NHS Hospitals Trust
OXMIS	Oxford Community Myocardial Infarction Study
OXVASC	Oxford Vascular Study
PAS	Patient administration system
PICI	Primary ischaemic cardiac injury
PVE	Acute peripheral vascular event
RI	Radcliffe Infirmary NHS Trust
SAH	Subarachnoid haemorrhage
SICI	Secondary ischaemic cardiac injury
STEMI	ST elevation myocardial infarction
TIA	Transient ischaemic attack
TOAST	Trial of ORG 10172 in acute stroke treatment
UA	Unstable angina
UK	United Kingdom
WHO	World Health Organisation

Chapter 1

Introduction

1.1. Purpose of study

The Oxford Vascular Study (OXVASC) is a study of all acute vascular events, transient ischaemic attack (TIA), stroke, acute coronary syndrome (ACS) including unstable angina (UA), myocardial infarction (MI) and cardiac death, and acute peripheral vascular (PVE) events in a mainly urban population in Oxfordshire. The pilot study covered a population of approximately 90,000 in nine general practices. The main purpose of the pilot study was to ensure that case-ascertainment was reliable before the main phase of the study. Data were also collected on patients undergoing elective vascular interventions (e.g. angioplasty, endarterectomy, bypass surgery).

1.2. Aims of main study

- To determine the incidence and case-fatality of acute stroke, acute MI, and acute PVE in the same population during the same time period.
- To determine time trends in incidence and case-fatality by comparison with previous Oxford-based incidence studies of stroke – the Oxfordshire Community Stroke Project (OCSP).[1]
- To perform case-control studies to compare clinical and molecular risk factors for stroke, ACS, and PVE, and to further identify those risk factors associated with specific pathological and aetiological subtypes of stroke.
- To perform case-control studies in patients with widespread atherosclerotic disease comparing clinical and molecular risk factors of cases presenting with acute thrombotic events with controls with no history of acute events (e.g. patients with stable angina, asymptomatic carotid stenosis, and stable claudication).
- To collect data on history of vascular disease in first-degree relatives of the incident cases to compare the genetic epidemiology of vascular disease in different territories. For example, we will determine whether the affected vascular territory(s) in first-degree relatives with symptomatic vascular disease predicts the vascular territory(s) affected in the proband.

1.3. Specific aims of pilot study

The specific aims of the first year of the study and of this thesis were:

- To refine the design of the study, make any necessary changes to the study forms and databases, and identify the most efficient methods of communication with the general practices and relevant hospital staff.
- To ensure that case ascertainment was reliable and complete.
- To examine the effects of case definition and quality of methods of ascertainment on measured incidence of stroke.
- To study the different definitions used for recurrent stroke and determined the effects of various definitions on the measured risk of recurrent stroke.

- To examine the role of a daily TIA and minor stroke urgent assessment clinic and determined the early risk of stroke after a TIA or minor stroke.
- To determine the risk of recurrence by aetiological stroke subtype (TOAST).[2]
- To make a provisional comparison of the overall incidence of stroke, ACS and PVE.
- To estimated time trends in incidence. All of the GP practices included in the pilot study were also in the OCSP. All the data collected contributed to the main study of temporal trends in incidence of stroke.
- To determine the overall burden of acute vascular events in Oxfordshire.

1.4. Why study the incidence, case-fatality and disability due to acute vascular events in a single population?

Arterial diseases are the leading cause of death and disability in the developed world, and are rapidly increasing in importance in the developing world.[3] Acute coronary syndromes (ACS) including myocardial infarction (MI) and stroke are the first and third leading causes of death in the developed world respectively, and the two most common causes of death worldwide. [3] However, mortality data underestimate the burden of vascular disease. Data from death certificates are often easily available in developed countries but may not be accurate. Comparison of OCSP and a population-based study of myocardial infarction (OXMIS),[4] suggests that mortality due to stroke is lower than that due to MI, but overall incidence is similar, and the total clinical burden of stroke may be greater. Stroke, for example, is the leading cause of neurological disability in the developed world[5] and a common cause of dementia, depression, epilepsy, falls and fractures. In order to allocate expenditure and set priorities for clinical services it is necessary to have data on the relative burden of different medical conditions.

High quality incidence studies provide greater detail on the burden of a particular disease than mortality data. However, these are expensive, labour intensive and

study populations need to be representative and reasonably large to make comparisons between studies and over time more precise.

Burden can also be estimated by measuring the long-term sequelae. For example, after a first stroke about 20% of patients will be dead within one month and a third remain dependent on others after a year.[6] However between stroke patients there is considerable variation depending on pre-morbid disability, initial stroke severity, stroke subtype and risk of recurrence. Knowledge of prognosis can allow estimates of the needs for assessment and diagnostic services both in the short and long term for community, out patient and hospital services.

Cost is another surrogate measure of the burden of the disease. However, both stroke and ACS impact considerably on areas that are difficult to quantify including costs to society from loss of national productivity, and cost to families from loss of income and subsequent need to take on the role of informal carers. Although direct hospital costs are important, the costs related to care for the subsequent disability is likely to be much higher.

The incidence, case-fatality, longer-term sequelae of TIA and stroke, ACS and PVE have never been measured in the whole population at the same time. This would provide an overall measure of the burden of atherosclerotic disease in a high quality population-based study. There is also uncertainty about the extent to which stroke, ACS and PVE share the same risk factors. There are known to be differences in their age and sex distributions, but little is known about the differential effects of other risk factors. Age- and sex-specific incidence data are required to guide service planning for the different needs of the population. A better understanding of differences in risk factors between stroke, ACS and PVE would allow preventive strategies to be targeted more effectively depending on the predominant pathology, would help to refine individual risk prediction models, and would help develop overall vascular prevention strategies. Type-specific data (TIA vs ischaemic stroke

vs primary intracerebral haemorrhage vs subarachnoid haemorrhage; STEMI vs NSTEMI vs unstable angina) is also important for detailed planning of the needs of a population. A formal comparison of incidence and outcome would also provide a firm basis on which local and national policy decisions about allocation of limited NHS funding for clinical services and limited governmental funding for medical research could be made. Rothwell has highlighted the considerable imbalance in research funding between stroke and MI.[7] NHS clinical initiatives also tend to give a higher priority to MI than to stroke. If funding for stroke is to be improved it is important that the burden of stroke is properly compared with more "high-profile" conditions such as MI.

1.5. Why measure time trends in incidence and sequelae of stroke and ACS?

Mortality due to stroke and ACS has fallen in most Western European countries and in some Asian countries such as Japan over the past few decades.[8,9] However there has been recent worrying trends to increasing mortality rates in Eastern European countries,[8,10] and a potential emerging epidemic of cardiovascular disease in developing countries.[11] However, the relative contributions of changes in incidence and case-fatality to mortality remain uncertain.[12] Few studies have been able to accurately measure time trends in a prospective population-based representative sample. In Rochester, Minnesota, where strokes have been systematically identified since 1945, there was an apparent fall in incidence until the end of the 1970s but this rose again in the 1980s.[13] However, the Rochester population has been criticised for not being typical of the rest of the USA.[14] This fall in incidence has been reproduced in other populations.[15-17] In contrast, incidence has risen in Sweden[18] and Denmark.[19] and has stayed the same in New Zealand,[20] Goteborg,[21] and Dijon.[22] Within these studies there may be additional differences depending on age and sex but the small numbers studied have not allowed precise analysis. For developing countries there is sparse information. The reasons behind these apparent changes in stroke mortality remain uncertain but various hypothesis including the role of successful primary prevention,[23,24] a decline in case fatality[25] and possible artefact

through changes in case definition and methodology over time[14] have all been speculated.

There are no data from the UK on recent time trends in age and sex specific incidence or disability rates for stroke and ACS. However, there have been major changes over the last 20 years in life-style, primary and secondary prevention treatments, and particularly in population demographics. Reliable data on the current and projected future burdens of stroke and ACS will allow future clinical and research funds to be targeted appropriately.

1.6. Why compare risk factors for stroke, ACS and PVE?

Little is known about the differences between risk factors for stroke and ACS. Compared with MI, stroke patients are generally older and there are some differences in the effects of blood pressure and cholesterol, and differences in haematological risk factors.[26,27] Moreover in previous studies, all strokes are often lumped together and it is increasingly recognised that stroke is a heterogeneous syndrome with each subtype likely to have different aetiologies, risk factors and prognosis. On the other hand, the mechanisms of instability and rupture of atherosclerotic plaque appear to be similar in different arterial beds.[28,29] However, more data are required. A better understanding of differences in risk factors would allow preventive strategies to be targeted effectively depending on the predominant pathology, would help to refine individual risk prediction models, and would help develop joint prevention strategies.

1.7 Why study factors associated with acute thrombotic complications of atherosclerosis?

There is a reasonable understanding of the processes that lead to the development of atherosclerosis, and some of the important risk factors, such as smoking, diet, lipid profile, diabetes and hypertension.[30] However, the risks of the major thrombotic and thromboembolic complications of atherosclerosis appear to be

related more to the stability of atheromatous plaques than to the extent of disease. Stable angina is associated with stable coronary artery plaques with a thick fibrous cap, whereas unstable angina, acute myocardial infarction and sudden cardiac death are associated with fissured or ruptured plaques.[31-33] Similarly, in patients with carotid artery atherosclerotic disease, plaque irregularity and rupture are closely associated with the occurrence of cerebral ischaemic events[34,35] and patients with irregular or ulcerated plaques on carotid angiography have a higher risk of ischaemic stroke than those with smooth plaques.[36,37] Although the blood flow dynamics at the carotid bifurcation are different to those in the coronary arteries, pathological studies of carotid plaques suggest that the processes of plaque destabilisation and rupture that lead to acute clinical complications are very similar.[34,35]

In order to reduce main clinical burden of atherosclerosis (i.e. risk of the acute thrombotic and thromboembolic complications), it is important that we understand the processes that control the stability of plaques. Local factors, such as sheer stress or vessel and plaque anatomy may be important,[38,39] but there is also evidence that some systemic factor(s) must be involved.[40] Potentially important factors include intra-plaque infection,[41,42] and genetic polymorphisms that influence the expression of cell adhesion molecules and lytic enzymes within plaques,[43,44] but it is likely that other mechanisms are also involved.

There is evidence that plaque stability is determined by non-traditional systemic factors. Rothwell and colleagues studied 5393 carotid bifurcation angiograms from 3007 patients with symptomatic carotid stenosis in the European Carotid Surgery Trial.[45] Patients with irregular or ulcerated carotid plaques were twice as likely as those with smooth plaques to have had a previous myocardial infarction and to have subsequent acute coronary events, but there was no difference in the risk of non-vascular events. Irregular/ulcerated plaque in the symptomatic carotid artery was also strongly associated with irregular/ulcerated plaque in the contralateral

carotid artery. These associations were independent of traditional vascular risk factors, and support the hypothesis that plaque stability in the carotid and coronary arteries are influenced in the same way by one or more non-traditional systemic factors.

It is important to try and distinguish between risk factors that are associated with the development of atherosclerosis, and risk factors associated with the development of plaque instability in patients who have established atherosclerosis. By comparison of patients who have widespread atherosclerotic disease but no history of acute events (e.g. stable angina, asymptomatic carotid stenosis, and stable claudication etc) with patients with acute thrombotic events, OXVASC has tried to identify clinical and molecular risk factors specifically associated with the development of acute thrombotic complications of atherosclerosis. OXVASC will determine dose-response relationships between potential risk factors and the predisposition to acute thrombotic events by comparing patients with no events, patients with one event in one vascular territory, patients with multiple events in one vascular territory, patients with events in two or more territories, and patients with multiple events in multiple territories.

1.8. Timescale

Year 1 (01/04/01 – 31/03/02)

Design of study, preparation of protocol, recruitment of researchers, selection of study general practices, and preparatory meetings with collaborating practices.

Year 2 (01/04/02 – 31/03/03)

Pilot case ascertainment study in nine general practices and start of follow-up study.

Years 3-5 (01/04/03 – 31/03/06)

Main phases of ascertainment study and follow-up study. Collection of data on appropriate controls from practice populations.

Year 6-10 (01/04/06 – 31/03/10)

Continued follow-up of study cohort, analysis of data from case-ascertainment study, and publication and presentation of results.

1.9 Conclusions

There is a need for up to date information on the incidence, case fatality and long term sequelae of stroke and atherosclerotic disease in general. This will provide the evidence required guiding appropriate resources for service provision. OXVASC will provide this data by studying all acute vascular events in the whole population at the same time.

This thesis has aimed to concentrate on the aims, methods and preliminary results from data collected in the first 18 months of OXVASC. For the incidence study (Chapter 9) I have analysed the full two year data. Throughout, I have concentrated on the analysis of data collected for TIA and stroke. However, a large amount of data on both patients with ACS and PVE has been collected over the last two years and there are a great deal many more future research opportunities.

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Chapter 2

Study methods I – Case definition and ascertainment

2.1. Plan of investigation

Case ascertainment was coordinated in collaboration with the Department of Cardiology (Dr A Banning), the Department of Primary Care (Professor D Mant), and the participating general practices. This phase included collection of blood samples and documentation of 30-day outcome. The follow-up study was co-ordinated with the Department of Primary Care (Professor D Mant and colleagues).

2.2. Why Oxford?

There are several reasons why Oxford was ideally suited for this study. However, the main reason for basing the study in Oxford was that we were uniquely fortunate to have previous Oxford community-based incidence studies of TIA and acute stroke (OCSP – 1981-86)[1] and acute myocardial infarction (OXMIS – 1993/4).[2] By using the same case definition and methods of ascertainment in OCSP we have

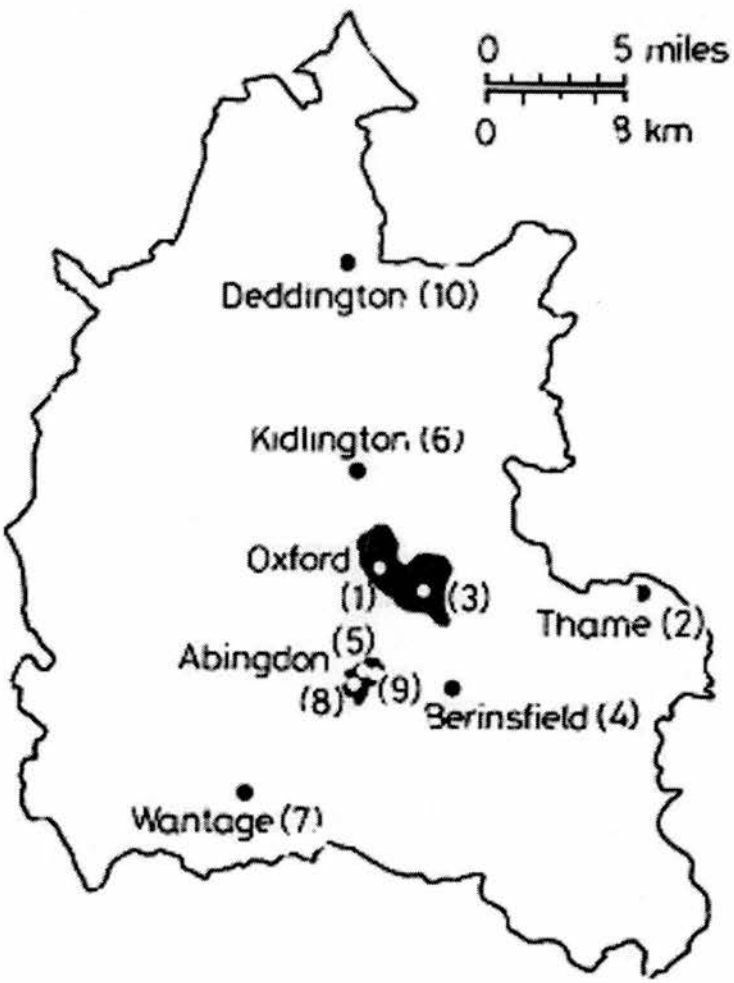
determined the time trends in stroke incidence and case-fatality. By comparison with follow-up data from OCSP, we will be able to determine time trends in disability rates and risk of recurrent vascular events. Comparison with OXMIS was more difficult because of the changing diagnostic citeria for myocardial infarction.

2.3. General Practices participating in pilot phase (Appendix 1)

A liaison GP was appointed in each collaborating practice to provide a continuous link between the ascertainment team and the practices. They assisted in identifying cases and reminded colleagues of the study. A liaison administrator was also appointed in each practice to assist with ascertainment, searches of GP databases and review of death certificates.

The pilot study (01/04/02 – 31/03/03) included 9 GP practices that were involved in the OCSP and OXMIS. Two practices (Thame and Deddington) that were involved in OCSP were excluded (Figure 2.1). Thame Medical Practice now refers also to Stoke Mandeville NHS Trust in Buckinghamshire. Deddington Health Centre now refers predominantly to the Horton General Hospital in Banbury in North Oxfordshire. For practical reasons our study was limited to using GP practices that referred to the Oxford Radcliffe NHS Trust Hospitals including the John Radcliffe, the Radcliffe Infirmary and the Churchill Hospital (ORH NHS Trust). Meetings with all GPs were held during the first two weeks in March 2002, and a pre-pilot run-in phase began on Monday 18th March. The main pilot study began at midnight on Monday 1st April 2002 and continued until Midnight Monday 31st March 2003. Enrolment of patients has continued thereafter in the main phase of the study.

Figure 2.1. Map of Oxfordshire with OCSP[1] and OXVASC collaborating GP practices



2.4. Study population

The population comprised all patients who were fully registered with 63 General Practitioners (GP) based in 9 family health centres who collaborated in the study. These same GP practices were involved in Oxfordshire Community Stroke Project (OCSP).[1] In the United Kingdom, patients register with a GP who provides their primary health care and, when necessary, refers them to secondary care. The GP receives all relevant information about specialist consultations and hospital admissions even if these do not occur locally. Thus the information held by the GP forms a lifelong record of all medical events as well as recording details of each consultation with the GP (including blood pressure recordings, blood counts etc). This individual record is transferred to a new GP if the patient moves residence. The collaborating practices were chosen if they: a) routinely referred patients to Oxford Hospitals; b) had an accurate computerised age-sex register (ASR) (Appendix 2); c) were willing to refer any patient with a suspected acute cerebrovascular event and; d) were computerised allowing searches for cerebrovascular diagnostic codes. The ASR provided accurate and up-to-date estimates of the denominator allowing easy identification of cross boundary flow and turnover within the population. The population was made up of predominantly Caucasian (94%) as well as Asian (3.1%), Chinese (1.5%) and Afro-Caribbean (1.4%).[3]

All patients in whom an acute vascular event was suspected were considered for inclusion. Patients were ascertained prospectively from hospitals and the community. For TIA and minor stroke not requiring hospital admission, case ascertainment was very similar to OCSP in that collaborating GPs notified the study office by telephone or facsimile of any patient whom they thought may have had an episode of acute neurological dysfunction caused by cerebrovascular disease. Patients who had a vascular event whilst temporarily away from Oxford were included, but visitors to Oxford who were not normally resident and registered with a GP were excluded. A liaison GP in each practice checked with colleagues regularly to ensure that all relevant patients were referred. Clinical data were obtained

retrospectively from case records, GP and relatives in those who died in the community. Registration of patients began on 1st April 2002 and continues.

Oxford has been criticised as a location for a study of vascular disease in that the population may not be representative of the UK as a whole ("too middle class") and was on average less socially deprived than elsewhere in the UK and results may not be generaliseable. Data to determine the level of deprivation at General Practice level is scanty. To estimate social deprivation amongst the population served by our practices we used an index of multiple deprivation.[4] This index is comprised of 6 domains – Access, Education, Employment, Health, Housing and Income with each domain containing at least 3 indicators from nationally available data. These data were available only at the level of electoral ward, of which there are 8414 in England. The lower the index the less deprived is the electoral ward. To ensure complete coverage of our population we used the electoral wards immediately surrounding our collaborating practices. The population of these electoral wards approximated to 180 000. The wards around our practices were significantly less deprived in comparison to the rest of England (mean Index of multiple deprivation score: 8.69 vs 16.98, Mann Whitney, $p<0.001$). However, our practices served a broad range of areas of deprivation with 2 serving electoral wards with ranking in the lower third nationally.

A proxy measure of deprivation is available at the GP practice level using low income scheme index (LISI) scores.[5] This is a measure of deprivation based on claims for exemption from the prescription charge on the basis of low income. The score is the cost of prescriptions that are exempt on grounds of low income as a percentage of the cost for all prescriptions. These figures are collected as part of a 5% sample of prescriptions for any practice with more than 1000 patients. The mean LISI score for our practices was 7.2% (Range 3.8 – 11.9) compared to an Oxfordshire average of 5.9% and a national average of 30.6%. However this score has disadvantages as it excludes the elderly to whom prescriptions are free.

2.5. Case definition and inclusion criteria

2.5.1. Acute cerebrovascular events

The definition of stroke was the same as in the OCSP.[1] Where new diagnostic techniques have been introduced (e.g. MRI scanning) cases were categorised as incident using the original OCSP definitions as well as on the basis of new techniques. All stroke cases were registered. Strokes were defined as "first-ever-in-a-lifetime" or recurrent. Neonates were not included.

The WHO definition of stroke was used[6]: rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and to those with subarachnoid haemorrhage), loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.

In fatal cases without clinical assessment the diagnosis of stroke was made only if there was clear autopsy evidence of recent acute infarction or intracerebral or subarachnoid haemorrhage as the primary cause of death.

In fatal non-autopsied cases, inclusion depended on a history of rapid onset with a clear focal loss of neurological function. Unless haemorrhagic it is recognised that stroke is an uncommon cause of sudden death.[7] In the event of any suspected stroke death, all available records were reviewed and the registered GP was interviewed to try to confirm or exclude the diagnosis. Inadequately described history without focal loss of neurological function or sudden death were not included as stroke events.

A TIA was defined as an acute loss of focal cerebral or ocular function with symptoms lasting less than 24 hours and which after adequate investigation was presumed to be embolic or thrombotic vascular disease.[8] Incident and recurrent events were registered. As in the OCSP TIA study,[9] our inclusion criteria were

designed to measure the incidence of TIA in the population whose TIAs come to medical attention. Our definitions were entirely comparable to OCSP. It required close collaboration with GPs to ensure complete ascertainment. TIA cases in patients with previous stroke were regarded as prevalent cases. Similarly if the patient had a recognised TIA prior to the study period, further events were regarded as recurrent. Incident cases were defined as any patient whose first TIA had led to medical attention occurring during the study period. TIAs occurring prior to the study period not brought to medical attention were ignored. If a patient had a further TIA during the study period that led to seeking medical attention the most recent event was taken as the incident TIA. If a patient had an event during the study period entirely similar to an event that had occurred prior to the study period but had not been yet diagnosed as a TIA, these events were regarded as prevalent. Patients presenting to their doctor during the study period with their first TIA but who had already suffered a stroke before or after the TIA were also excluded from the incidence TIA study to ensure complete comparability with OCSP and to avoid biasing prognosis. It is recognised that there is considerable inter-observer variability in the diagnosis of TIA.[10] Inter-observer reliability was optimised by rapid assessment of patients (median 3 days), cases were all discussed by two study physicians and to ensure direct comparability with OCSP, all cases were discussed with OCSP lead investigator, Professor Charles Warlow.

Cases of all possible cerebrovascular events were reviewed. This included a number of conditions that are often not included in TIA and stroke incidence studies. These cases were identified to assess the potential burden of cerebrovascular disease. Moreover, these 'possible' cases were followed up to determine their prognosis and risk of further vascular events. This included cases of retinal artery occlusion, subdural haematoma, venous and spinal stroke. We also identified cases of hemisensory syndromes (sudden onset of symptoms affecting one side of the body, including head and both limbs with no evidence of a neurological cause on brain imaging), isolated cranial nerve palsies, isolated diplopia and dysarthria, amnestic

syndromes not typical of transient global amnesia and non-arteritic ischaemic anterior optic neuropathy. Bilateral blindness was not included in the OCSP TIA study but subsequent analysis showed this to have a similar prognosis to definite TIAs.[11] These were registered. Once sufficient numbers of these cases have been registered, it is hoped they can be compared in case-control studies with definite cerebrovascular events to evaluate their prognosis. These events were not included in any incidence comparisons with OCSP data (see Chapter 4).

2.5.2 Acute coronary syndrome

Acute coronary syndrome (ACS) incorporates the full spectrum of possible acute presentations of ischaemic heart disease secondary to atherosclerotic coronary artery disease including unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). Specifically, STEMI is diagnosed with an appropriate history, ST segment elevation of one or more millimetres seen in two contiguous limb or two or more millimetres in chest leads on an electrocardiogram (ECG) or new left bundle branch block and / or one or more positive cardiac biochemical marker of cardiac necrosis. This includes posterior myocardial infarction diagnosed with at least 2mm ST depression in two consecutive right ventricular (V1, V2, V3) chest leads on ECG. NSTEMI is diagnosed with an appropriate history in the presence of one or more positive biochemical marker of necrosis without new ST segment elevation.

There is no universally accepted definition of unstable angina (UA) but it is thought of as a clinical syndrome between stable angina and acute myocardial infarction. Unstable angina was defined clinically as having a number of possible presentations: symptoms of angina at rest (usually prolonged > 20 minutes; new-onset (< 2 months) exertional angina or recent (< 2 months) acceleration of angina that is clinically more severe, more prolonged; or more frequent based on a pre-existing stable pattern resulting in admission to hospital with no rise in cardiac markers of necrosis.[12]

Myocardial infarction (MI) was defined in three ways to assess the impact of varying definitions on the burden of coronary artery disease in a population-based study:

1. Clinically: Based on the discharge diagnosis assigned by physicians under whose care the patients were assigned.

2. Epidemiologically: Based on the WHO definition[13] requiring two of three of symptoms, electrocardiographic findings and peak values of conventional enzyme activities (CK-MB, CK, AST, LDH), autopsy findings, history of coronary artery disease and history of previous MI. A definite MI was defined when:

- A diagnostic Q wave developed or ST elevation was followed by T wave inversion in serial electrocardiograms.
- Symptoms were compatible with MI (chest pain or its equivalent) and any one of the conventional enzymes was increased to > 2X the upper reference limit and serial ECG changes showed ST-segment or T wave changes.
- A recent infarction or an occlusion of a coronary artery was found in cases of fatal MI at autopsy.

A probable MI was defined as one of the following:

- Typical symptoms of chest pain > 20 minutes with either ST or T wave changes.
- Typical symptoms of chest pain > 20 minutes and any one of the conventional enzymes increased to more than the upper reference limit but remained <= 2X this limit.
- Atypical symptoms with both appropriate ECG and enzyme criteria.

In autopsied cases the diagnosis of probable MI was made if coronary artery disease was verified at autopsy and no other cause of death was found.

In fatal cases that did not undergo autopsy examination, a probable MI was defined as symptoms that were typical, atypical, or inadequately described if there was a history of previous coronary artery disease before death and no other cause of death was detected.

A definite or probable MI was excluded if serially measured conventional enzyme activities remained within normal limits and no evolution of Q wave abnormalities occurred in serial ECGs. If there was insufficient information these cases were excluded from the analysis.

3. European Society of Cardiology (ESC) and the American College of Cardiology (ACC) criteria[14] based on the use of more sensitive and specific markers of cardiac necrosis such as troponin I or T or CK-MB into a new definition of myocardial infarction.

Acute MI was defined as the presence of a biomarker of cardiac necrosis with one of:

- Ischaemic symptoms
- New Q waves
- Ischaemic ECG changes
- Coronary intervention.

An established MI was defined as new Q waves and two of the above.

Patients were defined as incident (first-ever) or recurrent. Patients presenting with UA with a previous history of MI were regarded as prevalent cases. A clear history of an event was required for inclusion and patients had to seek medical attention with symptoms compatible with an acute coronary syndrome. Suspected MI diagnosed on the basis of an ECG done for other reasons or an echocardiogram

showing a wall motion abnormality were not included. Patients with ECG changes or raised cardiac enzymes post-procedurally were included to determine the entire burden of ACS. If an area of myocardial scarring was recognised at autopsy, notes were reviewed to ascertain whether a MI had been recognised during life. If there had been no documented previous MI, the cardiac event leading to death would be regarded as incident. Precipitating factors leading to excessive cardiac demand were identified including inappropriate tachycardias, surgery and inotropic dependent states.

2.5.2.1. Acute coronary syndrome – special considerations

The ability to measure the cardiac specific protein markers, cardiac troponin T (cTnT) and cardiac troponin I (cTnI), has caused a paradigm shift in the assessment of patients with ACS. Troponin measurement in ACS patients identifies prognostically important myocardial damage when MI is excluded by conventional cardiac enzymes.[15] This has led to the proposed redefinition of acute MI,[14] recognising troponin measurement as the biochemical diagnostic 'gold standard'. The use of these biomarkers have been incorporated into management guidelines[16,17]

The prevalence of MI is dependent on the diagnostic criteria used. Other studies have shown that troponin is elevated in 15% of patients with suspected MI in whom conventional enzyme activities remain within normal limits.[18] Such an apparent increase in the number of patients diagnosed as MI may lead to a reduction in overall mortality. The adoption of troponin in the routine diagnostics of MI has been shown to 'increase' the diagnosis by 33% compared to a clinical diagnosis and by 23% compared to an epidemiological diagnosis.[19] The ESC/ACC has suggested that WHO MONICA should retain the established definitions of MI but simultaneously use their MI definition to compare the effect of diagnostic classifications on the epidemiology of coronary heart disease. Such a change would produce not only major implications for epidemiologists and service providers with many more patients potentially labelled with a diagnosis of myocardial infarction. Moreover,

the WHO definition implies MI can be diagnosed without biochemical evidence of myocardial necrosis while the ESC/ACC criteria mandate that troponin be elevated and subsequently be shown to fall. Such changes in definitions may have major epidemiological consequences.

Clinically troponins do have their limitations.[20] They take several hours to rise, peaking at 12-24 hours so values on admission may be misleading and if initially negative a second troponin measurement should be performed 6-12 hours later. Values may remain elevated for 2 weeks, limiting their usefulness in diagnosing reinfarction.

Biochemically there is uncertainty about the robustness of the troponin assays particularly between the different assays for cTnI that use different antibodies.[21] Different cTnI methods do not always agree and may be measuring different troponins. Moreover, reproducibility over time could also vary. The recommendations from the ACC/ESC document were for a diagnostic cut-off corresponding to the 99th centile of a normal reference population. Current assays are unable to detect troponin in the majority of normal healthy individuals. This has led to the proposal that an analytical target of percentage coefficient of variation of 10 (%CV of 10) is used as the cut-off for normal. This allows accurate separation of the cardiac and normal populations. However improved assay performance has paradoxically increased the number of patients with detectable troponin values without a clinical diagnosis of MI. 'Normal' ranges are often determined by manufacturers by testing in young adults with no evidence of coronary disease. It may be possible to define for the general chest pain population a low level of troponin that does not correspond to a clinically significant degree of risk. The level of troponin that can be reliably measured by the laboratory can then be used as the cut off point for definite myocardial damage. This corresponds to the functional sensitivity (%CV of 10) for the assay. Levels below this and above the detection limit of the assay indicate possible myocardial damage and should be repeated.

There is increasing evidence that troponin may be released in a range of other clinical conditions, including stroke,[22] subarachnoid haemorrhage,[23] pulmonary embolism,[24,25] and patients who are critically ill,[26] including septic shock.[27] Indeed troponin I rises have been attributed to tachycardia, congestive cardiac failure and pericarditis in patients despite having normal or only mild coronary disease on coronary angiography.[28] Similarly minor rises have also been demonstrated in muscle disorders, cardiomyopathies and chronic renal failure.[29] Owing to these concerns, some authors have urged caution in the wholesale adoption of troponin measurement to redefine myocardial infarction.[30]

However, there is no evidence that these troponin rises are false positive results. A recent editorial[21] stresses that cardiac damage does not necessarily equate to myocardial infarction. Acute MI remains a clinical diagnosis for which laboratory measurement is required for diagnosis but is not the sole arbiter. It is recognised that ACS arise from rupture of the atheromatous plaque resulting in platelet thrombosis and subsequent distal embolisation with micro-infarction.[31]

Elevations of troponin can occur without primary ischaemic cardiac injury due to secondary ischaemic cardiac injury (SICI) not caused by primary plaque rupture such as can occur during cardiac procedures through direct cardiac damage. Post-procedural elevation of troponin and CK-MB are related to the incidence of subsequent cardiac events.[32] Secondary ischaemic cardiac injury can also occur in any situation with supply-demand mismatch, for example pulmonary embolus. This may reflect underlying coronary disease but whether this is caused by ischaemia and necrosis or ischaemia alone remains to be determined. In non ischaemic cardiac injury (NICI), troponin rises may occur with direct myocardial involvement in the primary pathological process such as might occur with myocarditis.

In OXVASC, we classified cases using ESC/ACC criteria.[14] Practically this was necessary as we identified cases on a daily basis using an electronically generated list of all patients undergoing troponin I measurement. The team in charge of the patient's care requested troponin measurement on suspicion of a cardiac event. In a proportion of cases, we requested standard cardiac enzymes (CK and AST) if troponin I was raised above the normal range. All these cases were discussed with Dr Adrian Banning, Consultant Cardiologist to confirm or exclude a diagnosis of MI and to make a clinical judgement whether the troponin rise was related to primary plaque rupture, or due to secondary ischaemic cardiac injury or direct myocardial pathology.

In 2000, troponin I was introduced as the main marker offered to detect cardiac necrosis in the Oxford Hospitals NHS Trust. One specimen was sent when the patient was first seen and a second was sent at 12 hours after onset of symptoms. If a second infarction was suspected the same protocol was repeated. Troponin I was regarded as abnormally raised if > 1 ng/ml using an Immulite 1 immunometric assay. There has been concern with lack of standardisation of troponin I assays that has led to inter-assay differences of up to 20-fold between assays. The assay used in OXVASC was reliable across different labaratories according to UK National External Quality assessment Service (UKNEQAS) data.[33] Measurement of other cardiac enzymes were not requested routinely. If measured, creatinine kinase (CK) and aspartate transaminase (AST) were defined abnormal if at least one reading was more than twice the upper limit of normal when measured within 72 hours or within 3 calendar days of onset of symptoms.

2.5.3. Acute peripheral vascular events

Acute peripheral vascular events (PVE) were also identified. We defined acute limb ischaemia as the rapidly developing, sudden decrease in limb perfusion, usually producing a new or worsening symptoms or signs and often threatening limb viability. This might occur in cases with known peripheral vascular disease or in a

previously asymptomatic patient.[34] Acute deterioration in claudication (claudication to 'short distance' claudication) can occur as a result of an acute event but this, by convention, does not qualify as acute limb ischaemia.

We also identified cases of critical limb ischaemia (CLI) to try and determine the burden of peripheral vascular disease. It is recognised that only small proportions of patients with intermittent claudication develop CLI.[35] However, CLI threatens the survival of an extremity, may cause lifelong pain and up to 60% undergo vascular intervention and within 1 year 25% will have a major amputation and 20% will be dead.[35] Critical limb ischaemia was defined clinically as that which endangers the leg or part of the leg. Clinically it required rest pain requiring regular adequate analgesis for more than two weeks or ischaemic skin lesions, either ulcers or gangrene. Arteriography or Doppler measurements to delineate the anatomy of the large vessel disease throughout the leg and foot were desirable, as patients often had multi-level arteriopathic disease. This clinical definition was compatible with Fontaine's classification of patients with stage III peripheral vascular disease with rest pain and stage IV disease with ischaemic skin lesions.[37] It is recognised that this definition encompasses a wide spectrum of cases and several attempts have been made to subdivide this group into high and low risk cases using resting ankle pressures and toe pressures.[38,39,40] All these post-Fontaine definitions have been critisised for using arbitrary subdivisions, and excluding large groups of patients by using different pressure definitions.[35] Clearly, the term critical limb ischaemia implies a chronic element and does not represent acute limb ischaemia. However, we included critical limb ischaemia in our analysis of the burden of atherosclerotic disease (See Chapter 10).

We also identified cases of acute aortic pathology, both thoracic and abdominal, including leaking or ruptured aneurysms.

Patients with acute mesenteric ischaemia and infarction were included.[41] Cases were ascertained through review of angiography registers and often through the bereavement office or mortality coding. Cases of chronic mesenteric ischaemia, ischaemic colitis and mesenteric venous thrombosis were not registered.

Patients were defined as incident (first-ever) or recurrent depending on whether there had been a previous documented episode of critical or acute limb ischaemia or aortic pathology. If a patient had an acute event with a previous history of critical ischaemia, the recent event was regarded as incident. An episode of critical ischaemia with a history of an acute event was regarded as a prevalent case. The majority of cases were admitted to hospital or referred for urgent angiography. The Consultant Vascular Surgeon caring for the patient confirmed all diagnoses.

2.5.4. Interventions for atherosclerotic disease

Patients were included if they attended for any coronary angiography including angioplasty or stenting procedures. Patients attending for coronary artery bypass grafting were also ascertained. Patients undergoing these procedures primarily for other reasons such as valvular heart disease, cardiomyopathy or work-up for renal transplantation or other surgical procedures were not included.

Those attending for any peripheral angiography including angioplasty or stenting procedures were included. Patients attending for any other arterial vascular surgical procedure including bypass, embolectomy, endarterectomy and amputation were also included. Patients attending for 'screening' for example of abdominal aneurysms were not included. Patients undergoing renal angiography were also not included.

Patients were identified and enrolled if they attended for cerebral angiography for routine review after endovascular procedures for survivors of subarachnoid

haemorrhage. Patients attending for carotid angiography or carotid endarterectomy were also identified.

Procedures carried out for non-atherosclerotic indications were not included for example venous or neuropathic ulceration. Patients undergoing amputation primarily for sepsis and secondary osteomyelitis were not included even if there was underlying macro or microvascular disease.

2.5.5. Acute vascular deaths in the community

A large number of patients with vascular disease particularly coronary disease die suddenly in the community and never reach hospital. GP records, death certificates, coroner's reports and post mortems were all scrutinised to identify cases of acute vascular deaths. An electronically generated list of all patients dying from stroke, ACS and PVE was provided on a quarterly basis by the Department of Public Health. These cases were all scrutinised. If a patient died rapidly we attempted to obtain an eyewitness account as well as reviewing information in all available medical records.

2.6. Summary of case ascertainment

Case ascertainment of stroke was as similar as possible to OCSP. Multiple overlapping sources were used for TIA and stroke, ACS and PVE so that the degree of completeness of ascertainment could be compared.[42]

2.6.1. TIA and stroke

Collaborating GPs referred patients with TIA or minor stroke to our fast track clinic. Patients with TIA were seen as many of these patients on further assessment are in fact strokes. ORH admission and A&E registers were reviewed daily. Patients referred for carotid and brain imaging were identified. Lists were reviewed for cerebral angiography and carotid endarterectomy procedures. Admissions to

rehabilitation wards were reviewed. Patients were identified from coding and death certificate data.

2.6.2. Acute coronary syndrome

We aimed to identify all patients presenting with ACS. The majority of these patients were admitted to hospital. A small number were managed at home or in care homes were identified through their GPs. Patients were identified through daily review of admission registers and troponin I list. We visited the Coronary Care Unit (CCU) daily. Patients undergoing coronary angiography or bypass surgery were identified. All hospital deaths were identified from the bereavement office and deaths in the community were identified through GP death certificates and the Department of Public Health.

2.6.3. Acute peripheral vascular events

Acute peripheral vascular events were identified through admission registers and daily visits to the vascular unit. We were informed of all patients referred to the Vascular Surgery team from other specialities and all patients presenting for vascular interventions were identified. Out of hospital deaths were identified through death certificate and Public Health data.

Each practice appointed a liaison GP, and a liaison nurse or administrator. They assisted in searching computerised records for patients with suspected cerebrovascular disease. The study team maintained frequent personal contact with liaison GPs. A pager was carried between 8am and 6pm from Monday to Friday. At other times contact with the study office was via an answer-phone or fax. A quarterly newsletter was sent to all collaborators. Our study nurse visited each practice on a regular basis twice per month. Regular contact was also made with local care homes. The majority of ACS and PVE patients were ascertained after hospitalisation. However if they were not admitted or unable to attend the clinic, they were invited to participate in the study and were assessed at home.

2.7. Specific methods of case ascertainment

Multiple overlapping sources of ascertainment were used to identify vascular cases. Search strategies for TIA and stroke, ACS and PVE complemented one another. Ascertainment was based in the community, clinic and hospital involving hot and cold pursuit (Table 2.1).

2.7.1. Hot pursuit

Hot pursuit aimed to identify acute vascular events or vascular interventions through the emergency and admission medical services and referral to the rapid access TIA and minor stroke clinic using a prospective ascertainment strategy. Cases were identified rapidly through specific search protocols and data collected by direct interview or by extracting case notes while the patient was still in care. Hot pursuit was useful for obtaining data on timing and informed consent could be obtained. This was labour and time intensive often involving daily review of cases to ensure diagnostic accuracy. Indeed patients and their notes were often moved around the hospital and ended up being chased in 'hot pursuit'. On a weekday basis there was:

- Rapid assessment TIA and minor stroke clinic

The following search strategies made up hot pursuit. The following registers were searched daily:

- Oxford Radcliffe NHS Trust (ORH) admissions registers
- JRH Accident and Emergency admission register
- List of all patients undergoing troponin I measurement

Each of the following units were visited on a daily basis:

- Bereavement Office

- Coronary Care Unit
- Cardiac Day Case Unit
- Cardiothoracic Unit
- Acute Stroke Unit
- Medical Admissions Unit
- Vascular Surgical Unit
- Visit to other wards as necessary

2.7.2. Cold pursuit

Cold pursuit was the opposite of hot pursuit with no direct involvement with acute medical services. Potential cases with suspected acute vascular events or vascular interventions were identified from routinely collected data. Hospital records were reviewed to consider for inclusion. Because hospital and GP diagnoses of MI and particularly TIA and stroke occasionally disagreed with standard criteria for definition of these conditions, an excess of potential cases were screened. This data were collected weekly, monthly or quarterly on a regular basis. Data were reviewed to identify unknown vascular cases. It was recognised that identifying cases through cold pursuit represented a challenge in obtaining informed consent from the patients.

2.7.2.1. Weekly Ascertainment Protocol

The Surgical and Cardiac Directorates and the Patient Administration System generated the following data:

- Vascular elective surgical and angiography list
- Mortality and morbidity data collected by vascular surgeons
- Coronary angiography list
- Clinic lists for other stroke physicians
- Weekly review of admissions to rehabilitation wards

2.7.2.2. Monthly Ascertainment Protocol

The following data were obtained:

- Peripheral angiography list
- Cerebral angiography register
- Brain imaging referrals
- Carotid Doppler referrals
- Discharge ORH coding data

The following were contacted on a monthly basis:

- Paediatric Neurology Registrar
- Paediatric Cardiology Registrar
- 'Silver Star' team for complex obstetric cases
- Local care homes
- GP practice visits to review death certificates and search GP databases

2.7.2.3. Quarterly Ascertainment Protocol

These data were collected from visits to the coroners office and mortality data were electronically collated and provided by the Department of Public Health:

- Coroner post mortem results
- Public Health Department mortality ICD-10 coding data
- Rapid access chest pain clinic
- Vascular surgery out-patient clinics

2.8. Details of specific sources of case-ascertainment

Using hot pursuit cases were identified and assessed as soon as possible following the suspected index event. Patients were reviewed on a daily basis to ensure early assessment and accurate diagnosis.

2.8.1. Oxford Radcliffe NHS Trust (ORH) admissions registers.

An electronically generated print out from the Patient Administration System (PAS) of all patients admitted to any of the ORH, including private wards from any of our collaborating GPs was scrutinised on a daily basis. Names, hospital number and location of all appropriate cases admitted in previous 24 hours were logged in our daily register. Patients admitted under orthopaedic, general surgery, paediatric and gynaecology specialities were not specifically reviewed unless other information suggested they may have had a vascular event (e.g. troponin I measurement, brain imaging). We reviewed the medical notes of all suitable cases from the admission register to identify acute vascular events.

2.8.2. John Radcliffe Hospital Accident and Emergency register.

PAS generated an electronic print out of all patients attending Accident and Emergency department in the previous 24 hours. This list also included a one word diagnostic label given at triage. We searched for patients admitted with labels of 'collapse', 'off legs', 'TIA', 'CVA', or 'stroke', 'arrhythmia', 'breathlessness', 'angina', 'heart attack', or 'MI', 'cardiac arrest' and 'PVD' or any othe label suggestive of an acute vascular diagnosis. If patients had been discharged, their notes were reviewed.

2.8.3. Bereavement Office

The JRH bereavement office manages all hospital deaths including those occurring in Accident and Emergency. This office was visited on a daily basis. The cause of death for all cases registered with our collaborating GPs was identified. For cases of acute vascular events, details were recorded and notes reviewed. Cases were logged to allow further data collection from next of kin at a later date. The Churchill Hospital and Radcliffe Infirmary offices supplied the names of all deaths occurring in these hospitals.

2.8.4. Coronary Care Unit

The coronary care unit (CCU) kept a register of all patients admitted to their unit that recorded details of registered GP. This register was reviewed on a daily basis. Most patients had already been identified via admission registers, but some patients had been transferred from other wards with a new diagnosis of ACS and these cases were subsequently identified.

2.8.5. Cardiac Day Case Unit

The cardiac day case unit was visited on a daily basis. Identities of all patients due to attend for cardiac investigation were available. Notes were scrutinised to identify the type of cardiac investigation – predominantly coronary angiography – and the indication for intervention. Only cases being investigated for atherosclerotic disease were included. Patients attending for angiography were often identifiable in advance when patients attended for pre-clerking. Once identified, these patients were invited to participate in the study and assessed in the unit on the same day as their pre-clerking. Occasionally patients were admitted to the private wards for angiography and these were identified through the admission registers. If they agreed, these patients were interviewed often on the same day as their procedure.

2.8.6. Cardiothoracic Unit

The cardiothoracic unit kept an accurate ward admission register complete with GP details. This register was reviewed on a daily basis to identify patients admitted for urgent or elective cardiothoracic surgery including coronary artery bypass surgery. Many of these patients would have already been identified through the admission register. Patients who had been referred from other speciality wards for cardiac intervention such as angiography with stenting were occasionally admitted to the cardiothoracic unit prior to discharge. Patients admitted for thoracic aorta surgery were also identified through this mechanism. Patients were usually invited to participate and assessed during their post-operative convalescence.

Table 2.1. Summary of case ascertainment

Search Strategy	Daily	Weekly	Monthly	3-monthly	6-monthly	Yearly
ORH Admission Register	X	.	.	.	.	
JRH A&E register	X	.	.	.	.	
Bereavement office	X	.	.	.	.	
Coronary Care Unit	X	.	.	.	.	
Cardiac Day Case Unit	X	.	.	.	.	
Cardiothoracic Unit	X	.	.	.	.	
Brain imaging	.	.	X	.	.	
Carotid Doppler	.	.	X	.	.	
ORH discharge data	.	.	X	.	.	
GP practice visits	.	.	X	.	.	
Local care homes.	.	.	.	X	.	
Coroner's office	.	.	X	.	.	
Public Health coding	.	.	.	X	.	
Chest pain clinic	.	.	.	.	X	
Vascular surgery clinics	.	.	.	.	X	
Rehabilitation wards	.	X	.	.	.	

Search Strategy	Daily	Weekly	Monthly	3-monthly	6-monthly
Peripheral angiography	.	.	X	.	.
Cerebral angiography	.	.	X	.	.
Paediatric Neurology	.	.	X	.	.
Paediatric Cardiology	.	.	X	.	.
Obstetric liason	.	.	X	.	.
Acute Stroke Unit	X	.	.	.	.
Medical Admissions Unit	X	.	.	.	.
Vascular Surgical Unit	X	.	.	.	.
Troponin I list	X	.	.	.	.
Other wards	X	.	.	.	.
Daily TIA / stroke clinic	X	.	.	.	.
Elective surgical list	.	X	.	.	.
Mortality & morbidity data	.	X	.	.	.
Coronary angiography	.	X	.	.	.
Other clinic lists	.	X	.	.	.
GP database searches	.	.	.	.	X

2.8.7. Acute Stroke Unit

A daily visit to acute stroke unit identified any new admissions from other wards. Most of these patients were known through the admission register. The staff also kept a record of any other stroke cases that had been referred for acute stroke care. Several stroke cases that had their event during their hospital admission were identified through this method.

2.8.8. Medical Admissions Unit (MAU)

The admission register identified patients admitted to MAU. Occasionally patients from other wards were transferred to the unit with medical problems. The notes of these patients were reviewed to identify patients with acute vascular events.

2.8.9. Acute Vascular Surgery Unit

The vascular unit kept a log of all patients admitted to their unit with GP details. This was examined on a daily basis to identify cases of acute PVE. Patients admitted for elective endovascular or vascular surgical interventions were also identified. Patients referred from other specialities for vascular intervention were often transferred to the vascular unit.

2.8.10. Troponin I measurements

An electronically generated list of all patients undergoing troponin I measurement was obtained on a daily basis from the Department of Biochemistry. This list also included GP details. In ORH, troponin I was the standard investigation for patients with suspected ACS. All patients from the study practices having this investigation were recorded in our daily logbook. Many patients had already been identified on the admission register. At times, GP details were not available. Using the hospital number, the PAS system was interrogated to identify the registered GP. All patients having troponin I measurement in ORH were noted including patients on other sites such as the Nuffield Orthopaedic Centre (NOC). For these latter patients it was necessary to contact the admissions office in the NOC to find out GP details. If

patients on other sites had an abnormal troponin I, medical staff caring for that patient were contacted to obtain any evidence of an ACS. If this was the case patients were visited and invited to participate in OXVASC. If patients had been discharged medical notes were requested for review. If troponin I was carried out by one of our study practices in the community, the GP was contacted and patient details recorded.

2.8.11. Daily Ward Visits

The notes of any patients identified via the admission registers or a raised troponin I on other wards or specialist units were specifically reviewed. This included any patients admitted to wards on other sites such as the Churchill Hospital or the Opthalmology, Neurology and Neurosurgery wards in the Radcliffe Infirmary. Occasionally patients with subarachnoid haemorrhage were admitted directly to the neurosurgical wards and were found through this mechanism. Patients transferred to rehabilitation wards in the Radcliffe Infirmary were also identified and their notes reviewed for acute vascular events.

2.8.12. Daily TIA / Minor Stroke Clinic

GPs were encouraged to refer all patients with possible acute cerebrovascular events to our rapid access daily TIA and minor stroke clinic. Patients were referred predominantly by facsimile or by leaving a message on the OXVASC answering machine. GPs could contact the study team directly via a pager. GPs provided demographic and contact details as well as summary encounter sheets for each patient. Patients with amaurosis fugax or retinal infarction were also referred directly from the Eye Hospital for further assessment if from one of the study practices. Patients were telephoned directly and an appointment was made at the earliest opportunity usually within two working days. Patients were seen each afternoon in Thomas Rowney Out-Patients in the Radcliffe Infirmary. Patients had a full clinical assessment, phlebotomy, ECG and CT scanning. Stroke patients had brain imaging on the same day. TIA patients had CT within a week. Carotid

Dopplers were organised within 72 hours. GPs were faxed a management plan within two working days with preliminary results of all investigations. All patients were seen in the clinic at one month for follow up. Subsequent follow up was arranged partly in collaboration with the Department of Primary Care at 3, 6, and 12 months.

Using cold pursuit, cases of acute vascular events and those undergoing vascular intervention were identified from routinely collected data collected weekly, monthly or quarterly on a regular basis. Data was subsequently analysed to identify any previously unknown vascular cases.

2.8.13. Vascular elective surgical and angiography list

The Vascular Surgery Directorate produced a weekly list of all patients with their hospital numbers planned for admission for elective angiography or surgery for the following week. This list was faxed on a weekly basis. The PAS system was used to check their GP details. If they were registered from our study practices their names were recorded in our daily logbook and they were approached when they were admitted. This included patients attending the Vascular Day Case Unit for angiography who were then identified on arrival, invited to participate in OXVASC and interviewed on the same day.

2.8.14. Vascular surgery mortality and morbidity data

Patients admitted under the care of all the vascular surgeons were recorded and discussed at their weekly morbidity and mortality meeting. This included patients referred while in hospital to the vascular team including those from other hospitals. This information was recorded and a list faxed to OXVASC on a weekly basis. The hospital number was used to identify their GP details. Suitable patients were reviewed and registered with the study.

2.8.15. Coronary angiography list

All patients attending for coronary intervention were recorded on a Cardiac Unit database. The names, hospital number and GP details including information on their procedure were recorded. The identity of all patients attending for coronary angiography was provided on a weekly basis. The majority had been ascertained through daily visits to the day case unit. Any patients not known to the study but registered with our study practices were recorded.

2.8.16. Clinic lists for other stroke physicians

A list of all patients attending the outpatient clinics of local stroke physicians was generated using PAS. Their hospital numbers were used to identify their GP details. If registered with our study practices, their notes were reviewed to ascertain any TIA or stroke events that had not been referred to our rapid access clinic.

2.8.17. Weekly review of admissions to rehabilitation wards

Patients requiring further rehabilitation were often transferred to the Radcliffe Infirmary Rehabilitation wards including the Stroke Rehabilitation ward. PAS generated lists of patients from our study practices admitted to these wards and their notes were subsequently reviewed.

2.8.18. Peripheral angiography register

The Radiology Department registered the demographic and GP details for all patients undergoing vascular intervention. This information was reviewed on a monthly basis to ascertain any patients having endovascular intervention. This search strategy identified cases that had been referred for further vascular investigation from non-vascular surgery teams and those referred for investigation of small bowel ischaemia. Once identified these patients were logged and subsequently invited to participate in OXVASC. If ascertained late, their cases were discussed with their GPs and they were subsequently invited to participate if appropriate.

2.8.19. Cerebral angiography register

All investigations and interventions for subarachnoid haemorrhage or primary intracerebral haemorrhage were carried out at the Radcliffe Infirmary. A register was kept of all patients undergoing cerebral angiography. This register recorded demographic details, hospital number and procedure undertaken. This register was reviewed on a monthly basis. Details were logged of any patients from our study area that had cerebral angiography. PAS was used to identify their registered GP. Patients were invited for study participation if registered with our GP practices.

2.8.20. Paediatric liaison

On a monthly basis both the Paediatric Neurology and Cardiology Registrars were contacted personally to request information on any children admitted or seen in outpatients with acute vascular events. It was assumed that these cases were so rare and would require such intensive investigation that they would have been remembered. Discharge letters from the unit were also reviewed. Other methods of ascertainment for these groups included brain imaging referrals and coding. In addition, regular contact was maintained with one of the Paediatric Neurology Consultants who held records of all the cases children who presented with stroke in the Oxford Region. These records were reviewed.

2.8.21. Obstetric liaison

In Oxford, all complicated pregnancies are managed by the 'Silver Star' team based at the JRH. This team has a centralised referral system and telephone contact. On a monthly basis the team was contacted and information was requested on any pregnancies complicated by acute vascular events.

2.8.22. Brain imaging

All patients who undergo any type of imaging are recorded on the ORH Radiology database. Searches were set up for any patients registered with our study practices, having brain or spine imaging, including CT, MRI or angiography. This list was

provided on a monthly basis. For previously unknown patients, a report of their imaging was generated which often included the indication for the scan. If there was a suspicion the scan was performed because of an acute cerebrovascular event the patient notes were reviewed. If no report was available, notes were reviewed. If any TIA or stroke patients were identified, they were invited for inclusion after consultation with their GP.

2.8.23. Carotid Doppler referrals

Many patients suspected of having acute cerebrovascular events were referred for carotid imaging including referrals from the Ophthalmologists, other stroke physicians, neurologists and cardiologists. The vascular laboratory provided copies of carotid imaging reports of any patient registered with our collaborating GPs. The notes of these patients were subsequently reviewed to ascertain any TIA or stroke cases. If this was the case, their GPs were consulted and the patients invited for inclusion if appropriate.

2.8.24. Coding data

All patients admitted or dying in ORH NHS Trust were ICD-10 or OPCS-4 coded for medical diagnoses and surgical intervention respectively. On a monthly basis, a list of all patients from our collaborating practices discharged or dying with an ICD-10 vascular diagnosis or coded as having an OPCS-4 vascular intervention was generated by the coding department (Appendix 3). This list was cross-referenced with any patients already identified using admission registers. The medical notes of any cases that had not been identified were scrutinised. Acute vascular event cases were invited to participate if their GP thought appropriate. The coding team also supplied data on all patients seen in the Oxford Eye Hospital Casualty Department with a diagnosis of amaurosis fugax, retinal infarction, anterior ischaemic optic neuropathy or visual loss unspecified.

2.8.25. GP practice visits

Collaborating GP practices were visited on a monthly basis. GPs were encouraged to continue referring all possible cerebrovascular events to the daily clinic. In the majority of practices, a list of all patients who had died was kept. On each visit, a search was made to ascertain any acute vascular deaths through review of these lists and searching through all the death certificates. Cases ascertained elsewhere could also be clarified. GPs were also encouraged to inform us about any vascular events that may have occurred or been investigated out of area. Pre-morbid data were collected on patients that had agreed to be enrolled in the study. These visits also provided an opportunity to feedback to GPs regarding the study. Their involvement was critical to the success of the study. On a six-monthly basis the GP databases were systematically searched for all patients who had been coded as amaurosis fugax, retinal infarction, TIA, stroke, myocardial infarction or peripheral vascular disease. If this search identified cases that were not known, their notes were reviewed and their GP interviewed to identify further acute cases. In many cases, this coding search identified patients who were on cerebrovascular or ischaemic heart disease registers who had events prior to the study period and thus were not eligible for the study. In other cases, such as TIA the diagnosis was less secure. This database search was useful for cases of MI or stroke that had occurred out of area or abroad. If cases were identified in this way they were discussed with the collaborating GP and subsequently invited for inclusion if the GP thought this was appropriate. Regular contact was also made with local care homes to ascertain any acute vascular cases that may have been managed in the community. However, these events were often also recorded on GP databases.

2.8.26. Coroners Office

All sudden or suspicious deaths or deaths abroad of an Oxfordshire resident were reported to the Oxfordshire coroner. The coroner holds records of all such patients in a written register. The office also holds any coroner reports and the results of any coroner held post mortems. This office was visited on a three-monthly basis to

ascertain any patients from our collaborating practices that had been referred to the coroner that had died of an acute vascular event. Their details were collected.

2.8.27. Department of Public Health

All deaths in England and Wales are recorded through a central register with the majority of cases having a unique NHS number. Cause of death is coded using ICD-10 and the registered GP is identified using a unique GP code (Appendix 4). These data are then passed on to Health Authorities and their local Department of Public Health. Data can then be updated in local hospital and GP databases. A list of all deaths occurring in Oxfordshire with a vascular ICD-10 code in any position on the death certificate was generated by the local Department of Public Health (Appendix 5). These anonymised data were provided on a three-monthly basis. Diagnostic codes were placed as 'underlying cause of death' corresponding to part Ia on the death certificate. Further codes were apportioned to 'cause of death (1)' to 'cause of death (7)' with cause of death (1) and (2) corresponding to part I b and I c on the death certificate. Cause of death (3) – (7) corresponded to those contributary causes of death but not causing death normally put in part II of the death certificate. Patients registered with our collaborating practices with a vascular diagnostic code in the 'underlying cause of death', 'cause of death (1)' and 'cause of death (2)' position were investigated in detail. The predominant vascular codes used were:

- I64 – cerebral diseases
- I219 – acute myocardial infarction
- I251 – atherosclerotic heart disease (often used for sudden death)
- I718 - diseases of arteries, arterioles and capillaries

I259 – chronic ischaemic heart disease was often used to denote heart failure secondary to ischaemic heart disease and was not included as an acute vascular event unless there was other supportive information from reviewing the notes that they may have had an acute vascular event. NHS numbers were cross-referenced

with cases already known to the study. If not known to the study, PAS was used to identify demographic details. If cases were not known to the hospital-based PAS, GP databases were searched using the NHS number to identify patients. When cases of acute vascular deaths were identified, their registered GP was interviewed and their GP and hospital notes reviewed to ensure diagnostic accuracy of cause of death and for further premorbid information. All patients included in the study were flagged to facilitate follow up.

2.8.28. Rapid access chest pain clinic

The coding department generated a list of all patients from our study practices who were referred to the Rapid Access Chest Pain Clinic. Review of the clinic database identified core risk factors and final clinical diagnosis. Cases of unstable angina or myocardial infarction were identified. There were very few patients who were not admitted and had thus been identified through hot pursuit.

2.8.29. Vascular surgery clinics

The coding department generated a list of all patients attending a vascular surgery clinic. All the letters of correspondence from these clinic visits were reviewed. The demographic details and clinical histories of any patients with suspected critical limb ischaemia were identified. The majority were subsequently admitted for vascular intervention and ascertained through other methods. A few who were not admitted were included in the analysis of burden of vascular disease. Cases of acute peripheral vascular events were all admitted.

2.9. Protocols for inclusion

All potential TIAs, strokes, ACS and PVE were assessed as soon as possible after notification in a dedicated clinic, in hospital or in their home. Information from patient interviews was subsequently entered on to a computerised database. Data were extracted from medical records for cases first identified only after death or

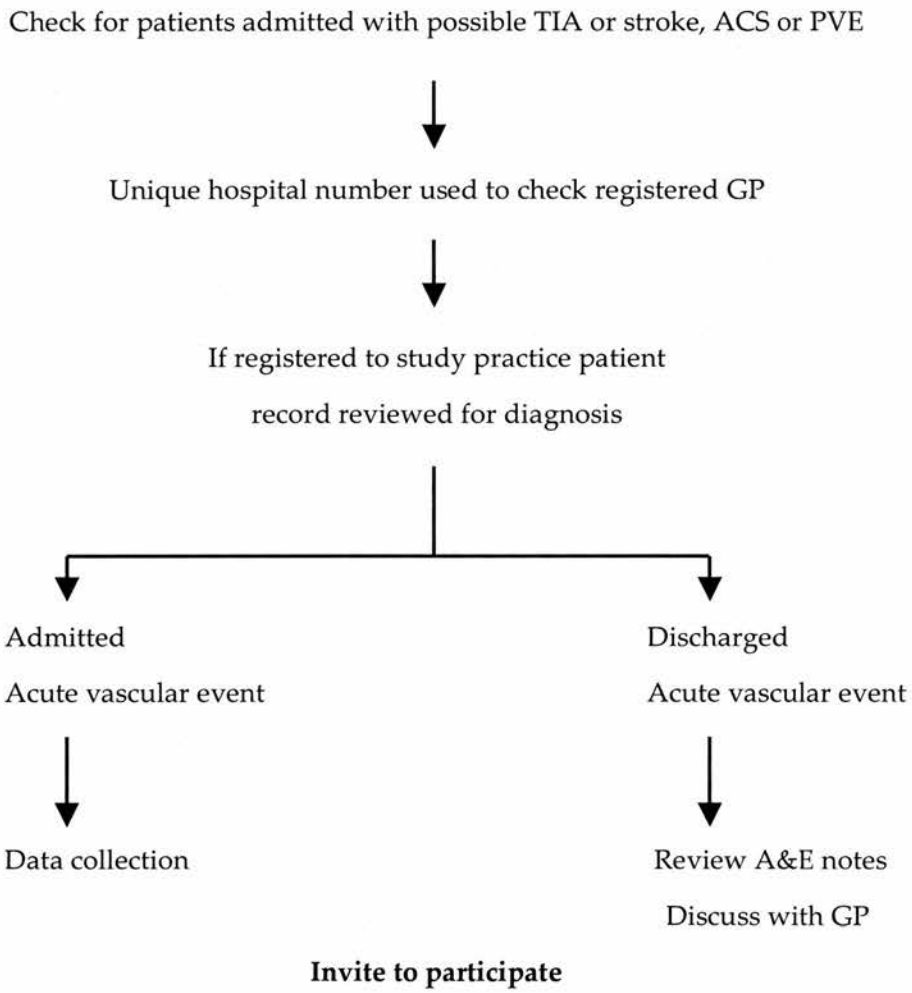
after a prolonged delay (e.g. if their stroke occurred whilst temporarily out of Oxford).

To facilitate assessment of patients at home or in care homes an equipment box was available consisting of mediswabs, vacutainers, needles, 10ml blood bottles, request cards, tourniquet, plasters, sharps box, and plastic specimen bags.

2.9.1. Accident and Emergency Register

On a daily basis the JRH admissions office generated an Admission Register for all ORH sites, an Admission Register specific to our collaborating practices, and an Accident and Emergency Register to identify potential study patients. The Admission Register for all ORH sites provides a means of locating cases already enrolled for continuing follow-up.

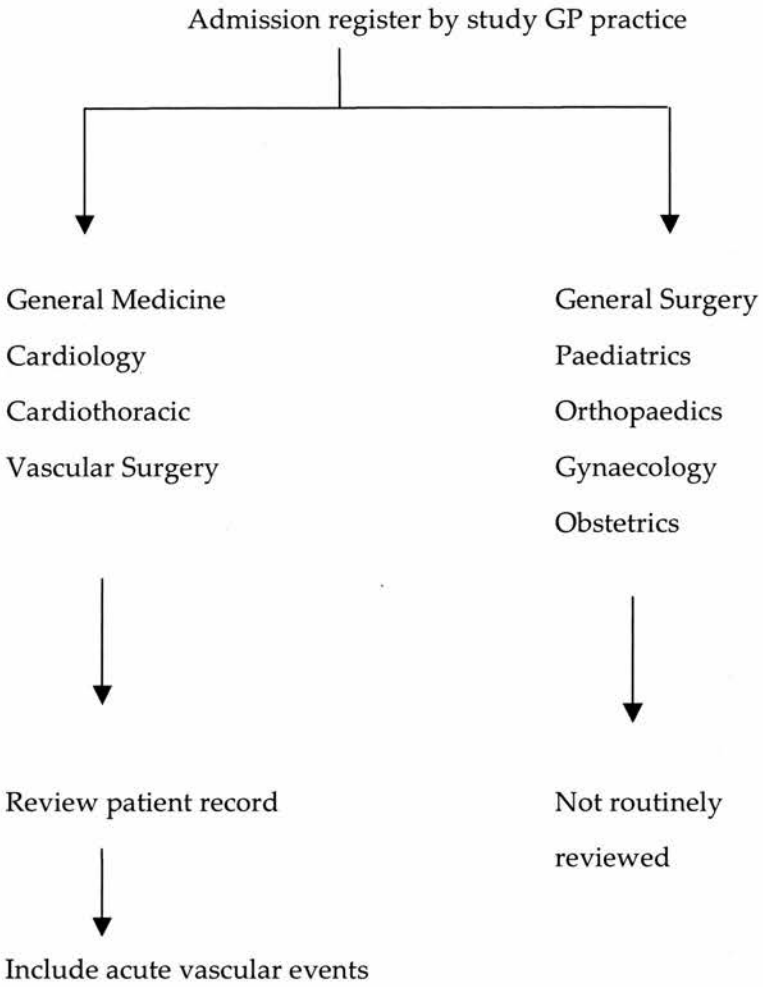
Figure 2.2. Protocol for using Accident and Emergency Register



2.9.2. GP-specific admission register

This daily list was generated of all in-patients of the ORH sites including the community hospitals specifically for our collaborating practices. This list was searched to identify any patients admitted in the 24 hours prior to the generated list. Lists on Monday morning were reviewed to record admissions over the weekend. This provided a patient name, unique hospital number, admission ward and consultant in charge of ongoing care.

Figure 2.3. Protocol for using practice-specific admission register

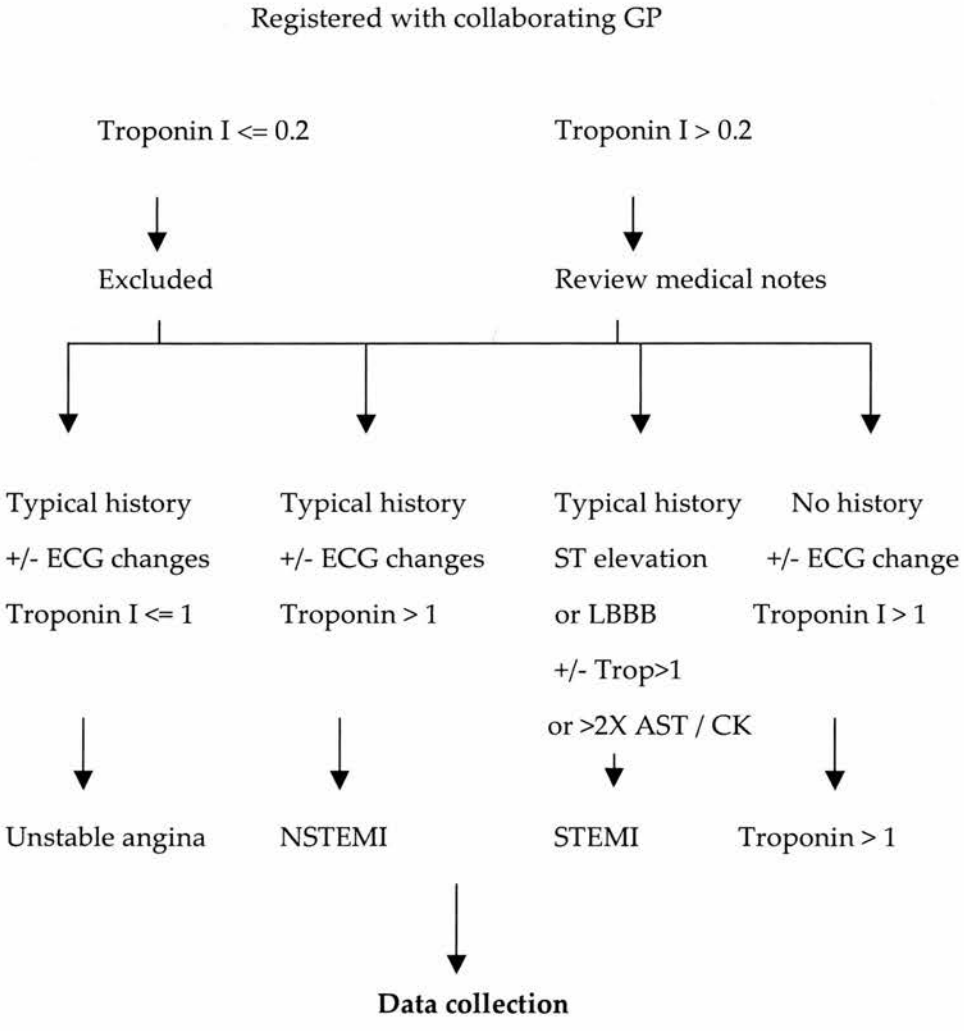


2.9.3. Troponin I list

The Department of Biochemistry generated a daily list of all patients having troponin I measurement to identify possible ACS patients. Some were already identified through the GP admission register and a daily visit to CCU. However patients admitted with other diagnoses subsequently developing ACS were ascertained. Cases of unstable angina, NSTEMI and STEMI were enrolled into OXVASC for further follow-up. Possible cases and those patients with raised troponin I but no other evidence of myocardial infarction were discussed with a

collaborating Consultant Cardiologist. If MI was diagnosed, these cases were subsequently invited to participate in the study.

Figure 2.4. Protocol for using troponin I list



2.9.4. TIA and minor stroke daily clinic

GPs were encouraged to refer all possible acute cerebrovascular events to our daily weekday TIA and minor stroke rapid access clinic based at the Radcliffe Infirmary. All cases were discussed with Dr Rothwell. Definite or probable TIA and strokes were enrolled into OXVASC. Possible TIA and strokes were also followed up using

the OXVASC protocol. All these cases were subsequently discussed with Professor Warlow – lead investigator in OCSP to ensure comparability with OCSP. Non vascular cases underwent a thorough assessment and were referred back to their GP for ongoing management or onto another speciality.

2.9.5. Late case ascertainment from cold pursuit

The majority of cases were ascertained from hot pursuit as hospital admissions or in the daily clinic. However, some were ascertained using cold pursuit methods some time after their acute event. Several TIA and stroke cases were ascertained through brain and carotid imaging referrals, coding data, searching of GP databases and the mortality file. Several ACS cases were identified if a troponin I had been measured in the community, by searching GP databases and the mortality file. Several cases of critical limb ischaemia were ascertained through review of the medical records of all patients seen in the vascular surgery clinics. Some of the vascular interventions were missed during their short stays in hospital as day cases. The hospital and GP records were scrutinised prior to consideration of inclusion. GPs were subsequently interviewed to assess the suitability of their patient for inclusion and interview. If felt unsuitable for interview, the history was discussed between two stroke physicians and a decision made on inclusion. If eligible, annonymised core risk factor data were collected from GP records. If the GP felt interview was suitable, TIA and stroke cases were telephoned directly and invited for assessment. ACS cases were written to, along with subsequent telephone contact if there was no reply. As we were offering a specialist assessment service we felt it was reasonable to contact TIA and stroke patients directly by telephone if we had the GP's permission. If patients did not agree to interview, permission was sought to record anonymised core risk factor data from their GP records and subsequent follow-up. Therefore patients had the option of 'picking and choosing' what type of assessment they encountered - interview, follow-up, record review alone or any combination.

Figure 2.5. Protocol for daily TIA and minor stroke clinic

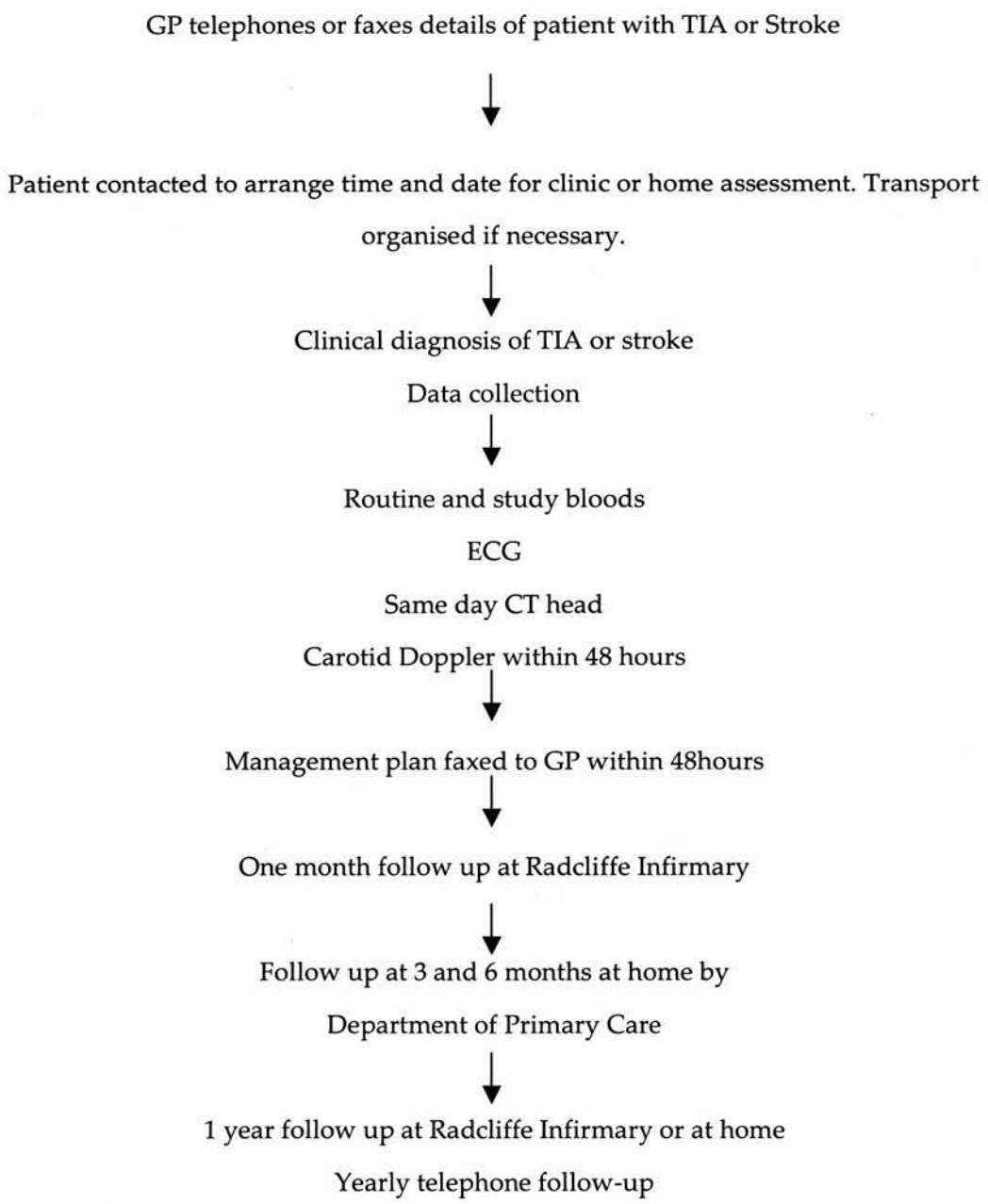


Figure 2.6. Case ascertainment of TIA and stroke using cold pursuit

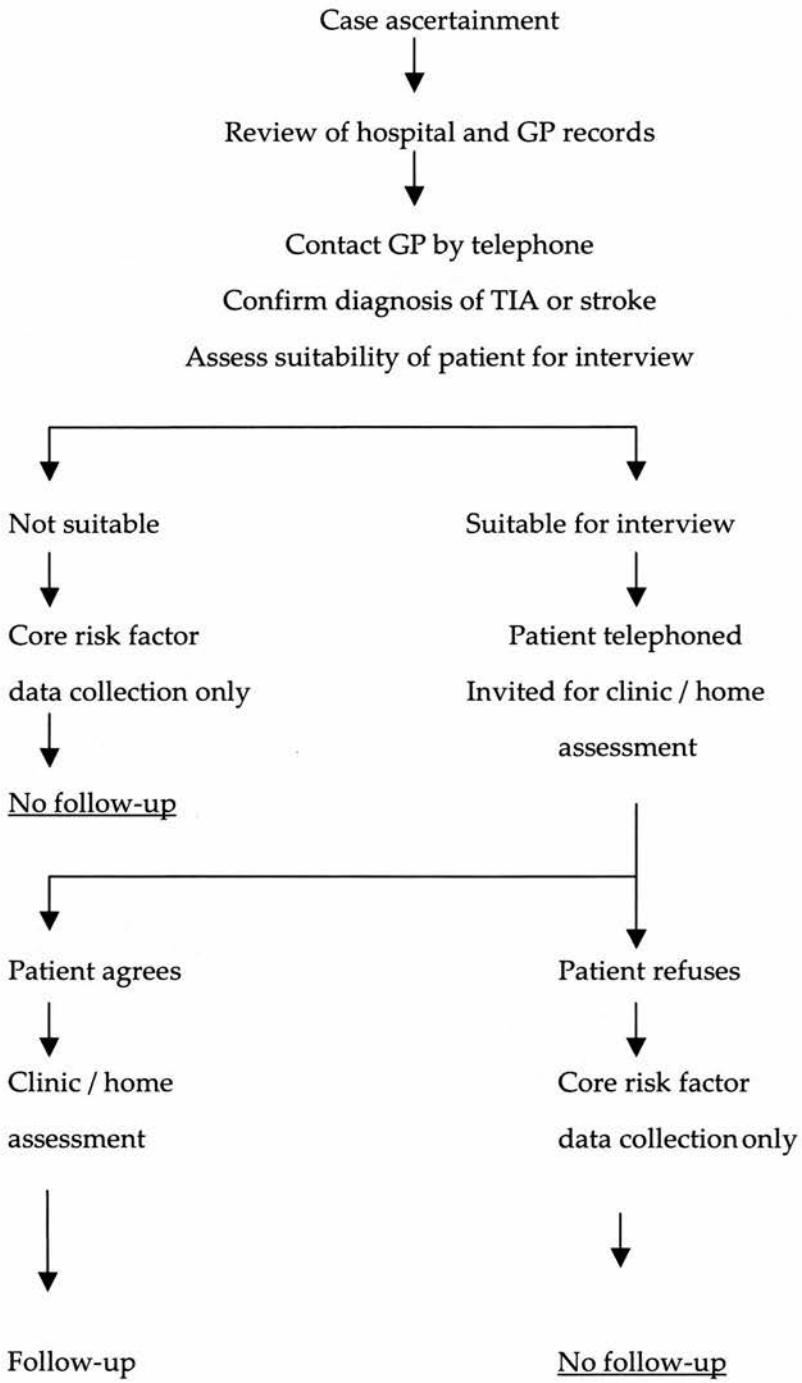
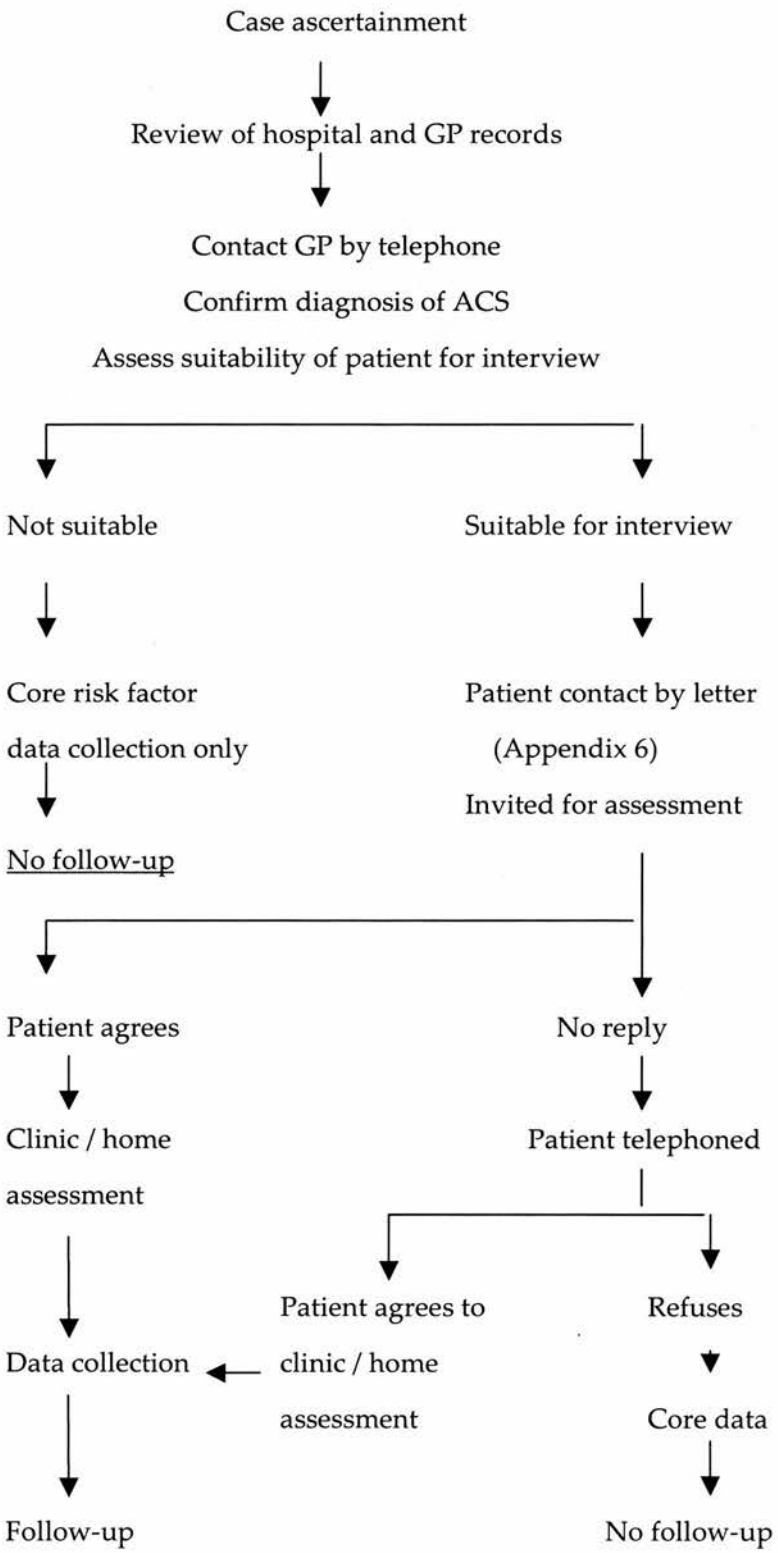


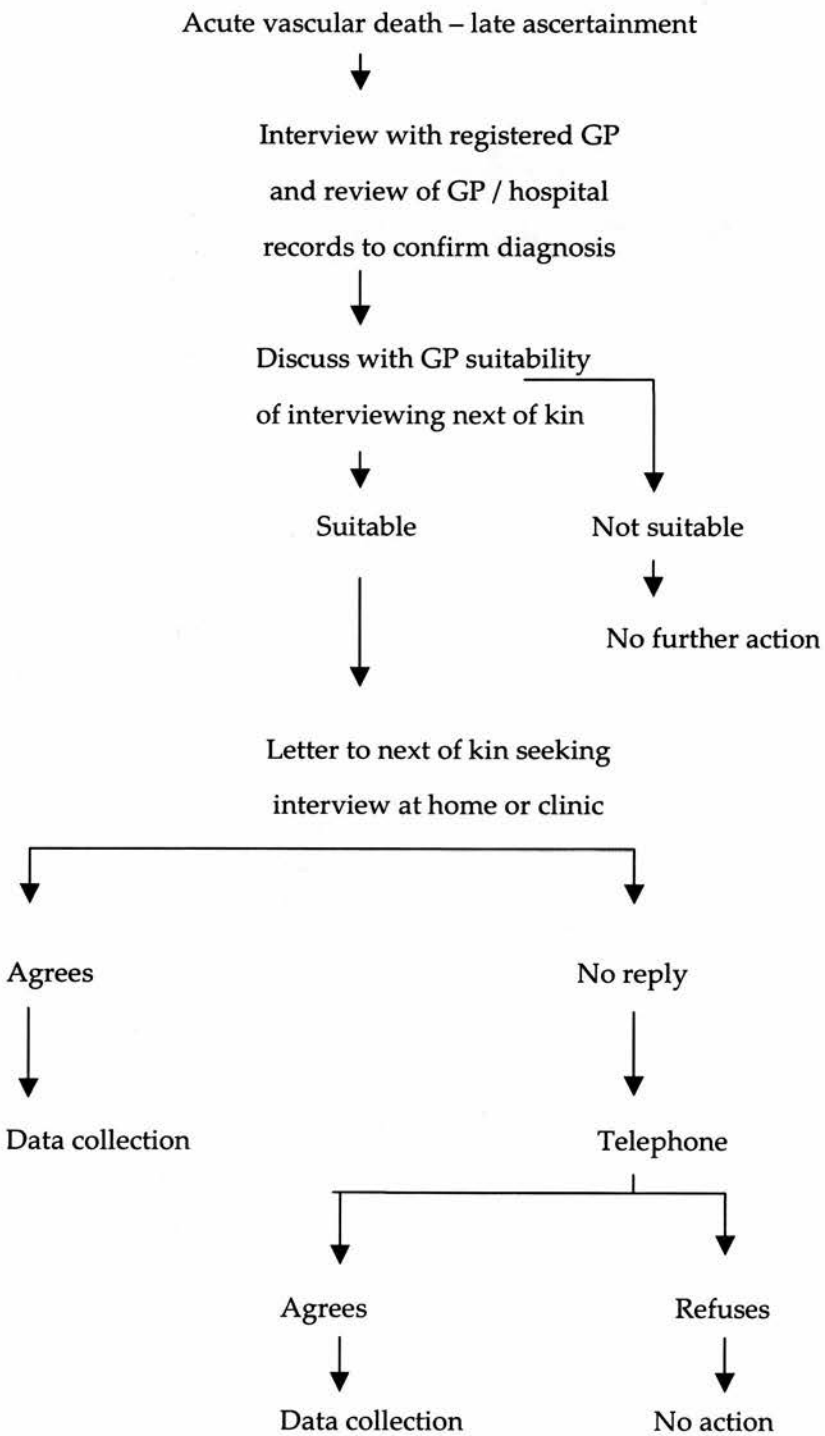
Figure 2.7. Case ascertainment of ACS using cold pursuit



2.9.6. Procedure for deaths in the community

It was envisaged that a significant number of potential OXVASC patients would die of their acute vascular events prior to admission to hospital, particularly those with ACS or intracerebral haemorrhage. The bereavement office was visited daily to ascertain any patients 'dead on arrival' to hospital. Death certificates from each study practice were examined on a monthly basis. The coroner's office and coroner post mortem results were reviewed on a three-monthly basis. Several intracerebral haemorrhages were ascertained as they had undergone urgent brain imaging prior to death. The Department of Public Health provided a list of all patients in our study practices who died and were ICD-10 coded with a vascular event. It is envisaged that the relatives of these patients wil be invited by letter and follow-up telephone call to provide premorbid information on their relative once a suitable time has elapsed (Appendix 7). Relatives were only invited to participate if the registered GP of the deceased believed this to be appropriate. Clearly this is important to ensure that data such as family history information is available for those who die suddenly in the community. This sensitive work was coordinated by a research nurse with an experienced background in community nursing. After a patient dies their GP notes are sent to central storage at the Thames Valley Health Authority headquarters. These notes were requested to collect further past medical history, supplement missing data on family history and ensure accurate diagnosis of cause of death.

Figure 2.8. Procedure for deaths in the community



2.10. Information Sheet

Patients were invited to participate in OXVASC. Patients and their carers were offered a verbal explanation of the study for both the ascertainment and the follow up phases of the study. A written information sheet describing both parts of the study was provided to the patient or their carer or relative (Appendix 8). The information sheet was read to patients who had problems reading due to stroke (visual field defect or alexia), or for other reasons.

2.11. Consent

If the patient was happy to make a decision about participation in the study immediately, then written consent was obtained (Appendix 9). If the patient required a period of time to consider the decision then this was respected.

Consent was more complicated in certain circumstances. Firstly, there were problems obtaining a normal signature from some patients with dominant hemisphere strokes. In such cases we tried to obtain a signature with the patient's non-dominant hand, and have this signature witnessed by a relative, carer or member of the nursing staff. Some potential participants were unable to give informed consent due to their neurological deficit, or other acute complication. In this situation, we attempted to contact the next-of-kin to obtain surrogate consent (Appendix 10). If the next-of-kin was not available we assumed consent for the purposes of recording basic clinical information from the medical records, but not for clinical examination or any venepuncture in excess of what was clinically indicated. The participant was informed that they were at liberty to abstain from participation in the study at any time.

Approximately 15-20% of stroke patients have some degree of either dysphasia or cognitive impairment. Surrogate consent is not legally well defined, but since our study is purely observational we thought that consent from next-of-kin was reasonable. This is standard practice in acute stroke research. Where consent from

neither the patient nor the next-of-kin was available, the Declaration of Helsinki[43] allows for research in this area if the specific reasons for not obtaining consent are reviewed by an independent ethics committee. Doyal[44] has argued that where informed consent is not possible, a common occurrence in stroke patients, then it should be clear there are important potential benefits from the research, and the risks of involvement should not exceed those associated with everyday life. If the research is epidemiological and medical records are to be used but consent cannot be obtained then this would be acceptable in light of potential benefits for patient or in the public interest provided confidentiality is maintained and there are no further consequences for the patient. Such research should be essential and permission granted from the patient's primary carer. Our study was approved by our local Oxfordshire Clinical Research Ethics Committee (OxREC C02.043).

2.12. Sample size

In the pilot phase, we expected to identify 40-50 TIAs and 175 - 200 first strokes (based on OCSP data).[1,9] 150-200 first definite or probable MIs (based on OXMIS definition)[2] out of 500-600 acute coronary syndromes, and 50-100 acute peripheral vascular events. In the main phase of the study, these numbers should increase five-fold. Within the original OCSP general practices we will have 80% power (alpha = 0.05, 2 tail) to detect a 16% reduction in the overall incidence of first stroke. All of our study practices are within the original OXMIS study area, and all incident MIs will therefore contribute to the study of time trends. We will have 80% power to detect a 10% reduction or increase in incidence.

2.13. Conclusions

Multiple overlapping sources of ascertainment were used to ensure accurate case ascertainment of all acute vascular events and those undergoing vascular interventions. This is the first time the incidence, case fatality and outcome of all acute vascular events have been measured in the same population at the same time.

Once eligibility criteria for inclusion had been met, patients were given information on the study. If they consented to interview, we proceeded to data collection.

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Chapter 3

Study methods II - Data collection

3.1. Data collection

Cases were ascertained as described and considered for inclusion (see Chapter 2). If patients were eligible for the study, a patient information sheet was provided and explained. Formal written patient consent or relative assent was obtained. If inclusion criteria were initially unclear then patients were reviewed on a daily basis to facilitate an accurate final diagnosis. Close liaison with the medical team caring for the patient was kept throughout. The patient was interviewed and examined within 48 hours of inclusion (usually on the same day). Data were collected by interview with the patient primarily, relative and review of medical notes. Data were collected using specific forms for each type of vascular event. The same core data were on all forms.

3.2. Data storage

Anonymised data were initially stored on paper copies of data collection forms labelled with a unique identification number and the ethics (COREC) approval reference number. Data collection forms contained demographic details including name and contact details for the patient and their next of kin. Details of registered

GP were also recorded. Paper copies of the data collection forms were kept in locked filing cabinets in the Stroke Prevention Research Unit.

Data were stored on a password-protected Excel spreadsheet. This had an administrative purpose with the unique identification number allocated to each patient starting at 0001. The same unique number was applied if a patient returned with another vascular event or intervention. Recurrences of any vascular event or procedure were identified and recorded. Date of birth, hospital number, NHS number and date of the study entry with GP details were stored. Cases were categorised according to their vascular event, timing of events and core risk factors were also recorded.

A Microsoft Access database was designed in parallel to the data collection forms to ease data entry and facilitate data storage. All data storage conformed to the Data Protection Act and was only accessible by study investigators.

3.3. Data collection forms

Data were collected using event-specific forms. Detailed data (timing, history of presenting condition, diagnostic information, and subsequent management) were collected on data collection forms for TIA and stroke (Appendix 11), STEMI (Appendix 12) and PVE (Appendix 13). The same core risk factor data were collected on all events including patients with UA or NSTEMI (Appendix 14) and vascular interventions (Appendix 15). Those cases with no typical history or ECG changes but a raised troponin I had core risk factor data recorded (Appendix 16).

3.3.1. Case ascertainment

Careful note was made of the methods of case ascertainment for each patient. When a suspected case was identified the source of such identification was recorded together with the date on which the case was identified. All subsequent methods of case finding were recorded. If ascertainment was delayed, the date on which the

information was received was recorded. For example copies of all brain imaging referrals were received on a monthly basis. The date of ascertainment for any case identified through this method was the date that these reports were received. The accurate recording of these methods of ascertainment allowed the application of the capture-recapture technique to assess completeness of ascertainment[1] (See Chapter 5).

3.3.2. History and timing of presentation

The history and examination were recorded as a brief narrative consisting of the salient points perhaps not well conveyed on computer database. Particular note was taken of any pre-existing disability, the speed of onset, any specific triggers or other associated symptoms.

Detailed information on the date and timing of the acute event and subsequent presentation to medical attention were recorded in 24-hour format. This included the date and time of event onset, initial call for assistance, first call to medical services, first seen by medical services, identification by the OXVASC team, admission if applicable and assessment. Detailed information was recorded on any progression of TIA and stroke cases within the first 24 hours and prior to presentation. From these data we have studied the effect of different definitions of recurrent stroke on the measured early risk of recurrence (See Chapter 6).

3.3.3. Potential triggers

The exact circumstances surrounding the onset of any acute vascular event were detailed in order to identify any triggering factors. Previous studies in this area have often been anecdotal, uncontrolled and tend to suffer from the possibility of recall bias. There may also be publication bias of positive results. However it is increasingly recognized that the onset of cardiovascular events follows a circadian periodicity with morning peaks in myocardial infarction, sudden cardiac death and ischaemic stroke.[2] Several case control and self-control studies have reported risks

of myocardial infarction two to six times greater during heavy physical exertion than during less strenuous activity or no activity particularly evident in persons who did not exercise regularly.[3,4] It is hypothesized that such events may trigger the disruption of coronary atherosclerotic plaques.[5,6] The highest level of activity before 30-120 minutes of onset of symptoms was recorded. To attempt to get control data the same question was asked for the contemporaneous 2 hours on the day before event. We used the following scale to classify levels of activity.

Minimal	Asleep or within 30 minutes of waking	3 METS
Light activity	Walking, golf	3-5 METS
Moderate activity	Mowing, digging, climbing stairs	5-7 METS
Heavy activity	Jogging, heavy work	>7 METS.

METS = metabolic equivalents required to perform the activity.
One MET is equal to 3.5 milliliters of oxygen consumed per kilogram of body weight per minute, the average value for oxygen consumption at rest.

In collaboration with the University of Oxford Environmental Change Unit, we plan to study any association between the onset of acute vascular events and seasonality and temperature. Any association remains controversial.[7]

3.3.4. Past medical history and vascular risk factors

Previous acute vascular events were recorded to assess whether the presenting event was first-in-a-lifetime or recurrent. A history of myocardial infarction was recorded based on patient, hospital or GP records. A previous STEMI was recorded only if the patient gave a history of having thrombolysis or ECG evidence in the medical record. Otherwise a documented history of MI was recorded as a NSTEMI. Any history of previous TIA or stroke was interrogated closely. Dates, duration and vascular territory of TIAs and strokes were judged from patient history and medical record. Critical limb ishaemia was not recorded as an acute event. Only if acute

PVE were previously documented would the notifying event be regarded as prevalent. Risk factors were recorded as present if known to patient or recorded in GP or hospital notes or on relevant medication for that condition.

Hypertension was defined as present if the patient or the medical record gave a history of high blood pressure for which the patient had been provided with treatment whether lifestyle changes or pharmaceutical management. Care was taken to ensure that where patients were on medication with multiple indications that hypertension was only recorded if these medications were being used for hypertension. All blood pressures taken over the ten years prior to the vascular event were collected from the GP record.

A history of diabetes was recorded including age of diagnosis, type of diabetes and treatment used. A clinical or echocardiographic history of valvular heart disease was recorded. Previous endovascular or vascular surgical interventions were also recorded.

Hyperlipidaemia was regarded as present if the patient or the medical records showed any evidence that the patient had been given lifestyle advice or drug management for lipid lowering. Moreover if patients were taking lipid lowering therapy even if this was for secondary prevention post myocardial infarction despite a 'normal' cholesterol then patients would be recorded as having a history of hyperlipidaemia. Pre-morbid blood pressures and cholesterol measurements were collected from GP records where available that will allow a more powerful analysis of the association of blood pressure and cholesterol with acute vascular events.

Any history of atrial fibrillation was recorded whether paroxsymal, persistent or permanent. Clinical or echocardiographic diagnosis of heart failure was recorded. Enquiry was made regarding migraine, epilepsy, peptic ulcer and chest disease.

Enquiries were made regarding a history of bleeding or clotting disorder and autoimmune disease. For women, history of pregnancy, miscarriage, menopause and use of the oral contraceptive pill (OCP) or hormone replacement therapy (HRT) was obtained. Information was obtained on age in years when any diagnosis was made. A detailed family history was obtained for any previous history of vascular events or risk factors. This was obtained from relatives if necessary.

Cigarette smoking (including "roll-ups"), pipe and cigar smoking were recorded. Patients were asked if they had ever smoked. For current smokers, the number of cigarettes smoked in a 24 hour day or the number of ounces smoked in a 7-day week and the number of years smoked was recorded. For ex-smokers, the calendar year when gave up smoking and the number of years smoked was recorded.

3.3.5. Medication usage

The names of all medications the patient was taking on a regular basis up to the time the event began were recorded. These were classified into therapeutic categories. Detailed information was collected on prior use of anti-platelet, anticoagulant or anti-inflammatory medication.

3.3.6. Modified Rankin scale

The modified Rankin scale[8] has been used extensively in both stroke trials and epidemiological studies. It measures independence rather than being task oriented and gives a better impression of self-care than disability indices such as Barthel and represents handicap rather than disability. Interobserver reliability has been reported as reasonable (k=0.56; weighted k=0.91) when completed by health professionals.[8]

3.3.7. Cardiovascular Rose Questionnaire

The cardiovascular Rose questionnaire[9] was used as a screening method to identify classical or typical angina in men aged over 35, myocardial infarction and

intermittent claudication.[10] It is a popular and simple screening tool and regarded as reliable, valid and reproducible. The questionnaire is highly specific (99.8%) in excluding healthy individuals but only moderately sensitive (67.5%) in detecting those with intermittent claudication.[10] The definitions of a positive classification are:

A Angina 'yes' to a and b, 'stop' or 'slow down' to d, 'yes' to e, '10 minutes or less ' to f. Site must include either sternum (any level) or left anterior chest and left arm. Grade 1 = 'no' to c, Grade 2='yes' to c.

B Possible infarction Yes

C Intermittent claudication 'yes' to a, 'no' to b, 'yes' to c and d, 'no' to f, 'stop' or 'slow down' to g, and 'usually disappears in 10 minutes or less' to h. Grade 1='no' to e, Grade 2='yes' to e

3.3.8. Barthel Index

The Barthel Index[11] was used to measure functional ability. It is based on observed functions. The scale covers feeding, mobility, personal toilet, bathing, continence and dressing. It omits tasks of daily living such as cooking and it was primarily designed for institutionalised populations. It is quick to score but is crude and may not be sensitive to improvements or deteriorations beyond the end-points of the scale (floor and ceiling effect) and within dimensions not represented by the scale.[12] However the scale has face validity and appears to assess ADL and correlates with other measures as expected and has predictive validity. Inter-observer reliability is generally high.[12]

3.3.9. Cognitive impairment

Folstein's mini-mental state examination (MMSE) was used to assess cognitive impairment.[13] The MMSE has been used extensively and has good inter-observer reliability. It takes 5 – 10 minutes to administer. The test covers orientation,

registration, attention and calculation, recall and language. The total score is 30 with the cut-off score of 23-24 suggesting cognitive impairment.

3.3.10. Informant Questionnaire on Cognitive Decline

There has been considerable interest in the relationship between vascular risk factors and Alzheimer's disease.[14] To determine the frequency of pre-existing dementia in patients with stroke in comparison to those with other acute vascular events, we administered an Informant Questionnaire on Cognitive Decline (IQCODE - Appendix 22).[15] It has been validated in elderly and Alzheimer patients using DSMIIIR criteria. It is made up of 16 questions scored on a five strand anchor of much improved (scores 1) to much worse (scores 5) given to relative or close friend. That person should have known the patient for 10 years and met them at least once a week. It consists of questions comparing the changes experienced by the patient over the last ten years in aspects of daily living requiring memory and other intellectual abilities. Global score ranges between 16 and 90. It has good interrater reliability and there is good correlation with MMSE.[15] It is not influenced by previous intelligence, educational level or social class.[15]

3.3.11. Onset anger scale

There have been several uncontrolled case series reporting an association between precipitating stressful events and anger and the triggering of acute vascular events. Previous studies have suggested a relationship between anger expression[16] and trait anger,[17] with the risk of incident stroke. However, such studies potentially suffer from confounding factors.[18] In the interview-based Determinants of Myocardial Infarction Onset Study,[19] Mittleman used a self-control design to apply an onset anger scale to patients with myocardial infarction. Patients were asked to report their state of emotion on a single item, seven-level, self-report scale. The relative risk of myocardial infarction in the 2 hours after an episode of 'anger' was reported to be 2.3. We used similar methods to collect these data for patients presenting with all acute vascular events. We also collected data for the same two hours time on the

preceding day. Patients were considered exposed if they reported a peak level of anger greater than or equal to level 5 (very angry, furious, enraged) during interval of interest 2 hours before event.[19] The control data were their actual exposure in the comparable 2 hour period at the same time on the same day before event. If the onset of event came on wakening, the time of waking up and events in 2 hours prior to going to bed were recorded.

3.3.12. Stress

There has also been considerable interest in the association of stress with acute vascular events. In the early 1990s the concept of type A coronary prone behaviour dominated thinking about psychosocial factors and coronary heart disease. Increasingly it has been shown that this concept is too diffuse and the concept of hostility has been implicated.[20] In the Caerphilly Study,[21] the association between a measure of psychological distress and the incidence of stroke was studied prospectively in a middle-aged group of men. Psychological distress was reported to be a predictor of fatal ischaemic stroke but not of non-fatal stroke or TIA. However, in a Danish study[22] of nearly 13000 subjects of all ages there was no significant independent association of self-reported stress intensity with risk of stroke. These studies are difficult to interpret from a methodological standpoint and in the definition of the nature of psychological distress.[23] The evidence for 'stress' being a risk factor for stroke remains inconclusive. 'Stress' may be more associated with behavioural differences with other high-risk behaviour or socioeconomic status. In an attempt to keep this area of interest simple and quick, all patients were asked what sort of person they thought they were in terms of a stressful personality. The interviewer also made a clinical judgement of the patient's stress level. Both patient and interviewer were given a choice of five responses between 'very relaxed', 'fairly relaxed', 'average', 'prone to stress', and 'highly stressed'.

3.3.13. Social networks

Social networks have been considered to be a risk factor for vascular disease but studies have often been poorly controlled for confounding factors. In a US study[24] examining association of low social networks with cause specific mortality and morbidity, 30000 middle-aged men were followed up prospectively. It was reported that social networks were associated with lower total mortality by reducing deaths from cardiovascular disease and accidents / suicides. Strong social networks have been associated with reduced incidence of stroke though not of coronary heart disease.[25] Data were collected on marital status and contacts with friends or relatives to determine any association between social networks and acute vascular events in our population.

3.3.14. Social history

Socioeconomic status is a powerful predictor of cardiovascular risk,[26] but the association with stroke is less certain,[27] as it is not clear whether these associations with an increased stroke risk can be accounted for by differences in health behaviour and vascular risk factors.[28] However recent reports using occupation as a measure of social class have suggested poor socioeconomic circumstances were independently associated with greater stroke risk.[29] Moreover, when an area-based deprivation score was used in a West of Scotland population, socioeconomic deprivation was associated with stroke risk factors and stroke at a younger age. Deprivation had an independent effect on baseline stroke severity.[30] In OXVASC, information was gathered on place of residence, most recent occupation, socioeconomic class, ethnic origin and age of leaving full time education. Social Class was coded using the Standard Occupational Classification Scheme.[31] If retired, the participants' last job was recorded. In the case of a child or a spouse who did not work the occupation of the father or partner was taken respectively.

3.3.15. Sleep disorders

An association between sleep disorders and vascular disease including stroke has been difficult to define. Studies in acute stroke are difficult to interpret as acute stroke is a common cause of irregular breathing. However in a recent case-control study examining the prevalence of obstructive sleep apneas among TIA patients there was no increased prevalence of disordered breathing in TIA patients.[32] Questions from a previously validated clinical prediction model incorporating some of the features of the Epworth scale were asked of all patients.[33] These questionnaires have been used to try and prioritise patients with sleep disorder for polysomnography. These models have shown reasonable sensitivity but lack specificity but do have a role in prioritising further investigation.[33] Hip, waist and collar size were all measured at assessment. Most recent weight, height and body mass index were collected from the GP records.

3.3.16 Nutrition and exercise

Observational studies have suggested a relationship between lifestyle factors including diet and the risk of cardiovascular disease and stroke.[34] However, such associations may be explained by confounding variables.[35] Previous observational studies have suggested the risk of stroke and coronary disease are associated with anti-oxidants,[36] low intake of fresh fruit and vegetables[37] and fish.[38] However a recent randomised trial of antioxidant vitamins in high risk vascular patients has showed no benefit.[39] The pre-morbid dietary lifestyle of patients presenting with acute vascular events was recorded specifically examining the intake of fish, fruit and vegetables, addition of salt and use of reduced fat milk.

Data now suggest raised homocysteine is a risk factor for vascular disease,[40] and treatment with homocysteine lowering folic acid supplements is currently being studied in a randomised controlled trial.[41] We have collected data on the oral intake of vitamin and mineral supplements.

Lack of physical exercise is associated with coronary events[42] and may be associated with stroke.[43] Participants were questioned on any physical exercise and a clinical judgement was made on the amount of exercise corrected for any pre-existing disability. The interviewer was given a choice of 'none', 'below average', 'normal' and 'above average'.

3.3.17 Depression

Depression may be an important prognostic factor after vascular events. However, the role of depression as a causative risk factor for acute vascular events has not been determined. Depression has been recognised as a poor prognostic factor for patients post myocardial infarction but it is unclear whether individuals with depression are more likely to develop coronary events over time.[44] Other studies have reported an association of increasing depressive symptoms over time with significant excess risk of death and stroke or myocardial infarction.[45] In two large prospective cohorts[46,47] pre-existing depressive symptoms were reported to be associated with a doubling of risk of incident stroke. Different studies have used different methods of diagnosing pre-existing depression. In OXVASC, the one question Yale Depression screen,[48] 'Do you often feel sad or depressed?' was used to screen for pre-existing depression. This has been shown to be as accurate as the Geriatric Depression Scale in screening for depression in a clinic setting[49] and in stroke patients.[50]

3.3.18 Life events

Previous studies have examined associations between the onset of acute vascular events and major life events and proposed a mechanism.[51] However, studies have been anecdotal, poorly controlled and results have been conflicting. A case control study looking at the association between stroke and severely threatening life events in the preceding year showed these events to be significantly more common in the stroke patients.[52] Similarly patients with myocardial infarction have been shown to have significantly more life events in the preceding 3 months than case controls.[53] In

OXVASC, patients were interviewed to determine preceding life events and the degree of stress caused to the patient was graded ('very much', 'moderately' or 'not too much'). It is envisaged that patients with other vascular events may be used as controls to determine any association between life events and stroke. In the next phase of the study, it is planned to enrol community controls.

3.3.19 General examination

All patients were asked if they would agree to a general examination including weight, height, hip, waist and collar measurements. Patients were examined for evidence of vascular disease including bruits and murmurs. Routine observations of temperature, pulse and heart rhythm, blood pressure were made. If admitted blood sugar and oxygen saturation were recorded.

3.3.20 TIA and stroke examination

Patients with TIA and stroke were given a thorough neurological examination and the National Institute of Health Stroke Scale (NIHSS)[54] was recorded. This is broader than the disability and handicap scales such as Rankin. It is a 15-item scale covering level of consciousness, pupillary response, gaze, visual loss, facial palsy, motor-arm, motor-leg, plantar reflex, limb ataxia, sensory loss, neglect, dysarthria, and language. It is observer rated and takes 5-8 minutes. Items have 3- or 4- point response scales, scored 0-3 (0=normal) Change is measured as same, better or worse. There is reasonable validity and inter-rater agreement, and the 7 day score is related to eventual outcome. However, it has been criticized for trying to summarise all impairments in a single score.

3.3.21 Prognostic models for acute stroke recovery

Prognostic models in stroke may be useful in clinical practice and research. In a recent systematic review,[55] the only variables shown in multivariate models to be independently associated with one year survival were cardiac failure, conscious level and the level of impairment at baseline whereas age was more important in

long term survival. Impairment and conscious level in the acute stage also influenced the functional outcome as did the degree of weakness, whereas younger age and urinary continence appeared to be important predictors of getting home. Counsell[65] points out however that many of the studies were of poor quality and interpretation had to be cautious. Tilling[56] has developed models of functional recovery after stroke to assist in predicting outcome using prognostic variables such as urinary incontinence, sex, pre-stroke disability and dysarthria along with age, dysphasia and limb deficit. Such models may assist in medical management during rehabilitation. More complex factors have also been examined. NIHSS score, time in hours from stroke onset to brain imaging and volume of ischaemic brain tissue on DWI MRI have been shown in combination to provide better prediction of stroke recovery than any factor alone.[57] In OXVASC, data consistent with the Royal College of Physicians stroke audit were also collected.[58]

3.3.22. Myocardial infarction

Data were collected consistent with the core dataset for myocardial infarction developed by the Royal College of Physicians and the British Cardiac Society.[59] ECGs were studied and reported. All cases of myocardial infarction were risk stratified using TIMI scores.[60, 61] All difficult cases were discussed with a Consultant Cardiologist for confirmation of diagnosis.

3.3.23. Peripheral vascular events

Data were collected on site, nature and management of acute PVE. This included cases of critical limb ischaemia who subsequently underwent peripheral angiography or other vascular intervention. Cases of acute peripheral vascular events related to acute on chronic thrombosis or embolic episodes were also identified as were cases of ruptured or leaking, abdominal or thoracic aorta.

3.4 Clinical management

Clinical progress was monitored for recurrent events or other complications. All relevant reports of investigations past and present including ECGs were photocopied. All subsequent treatments were recorded including lifestyle advice, drug treatment or further vascular interventions. If admitted then length of stay and discharge destination were recorded.

3.5 Procedure for blood collection

3.5.1. Routine blood investigations

For patients attending the TIA and minor stroke clinic blood was taken for routine investigations including urea and electrolytes, liver function tests, calcium and albumin, thyroid function tests, C reactive protein, random glucose, lipid profile, full blood count and erythrocyte sedimentation rate (ESR). Autoimmune profile, clotting and thrombophilia screening were carried out if indicated.

For TIA and stroke patients under the care of other medical teams no additional blood investigations were requested by the study team but the investigations carried out by the medical team were recorded. For a proportion of patients with NSTEMI or STEMI, serial cardiac enzymes were requested retrospectively to allow comparison with OXMIS.[62]

3.5.2. Study blood

Patients attending the clinic for assessment and those admitted with an acute vascular event (TIA, stroke, STEMI, PVE) who consented to the study had the following samples collected at the same time as clinical bloods:

- 1 x plasma (green)
- 1 x serum (yellow)
- 2 x EDTA (purple)
- 2 x citrate (blue)

Serum, plasma and citrate blood samples were centrifuged for 10 minutes at 4000 revolutions per minute. The supernatant was stored in plastic cryotubes. Whole blood was also pipetted into cryotubes. Each was labelled with a unique identification number, recorded in the specimen logbook and frozen at –85 ^{0}C.

If patient has been on aspirin prior to admission, the two citrate blue samples were sent directly to Haemophilia Centre at Churchill Hospital. The date and time of collection was stated clearly on the red haematology card, together with the date and dose of the last aspirin taken prior to collection. Any other anti-platelets or anti-coagulation or statins were also recorded (Fragmin, Streptokinase and/or TPA).

Patients with unstable angina did not have any study blood taken. Patients admitted with NSTEMI had two citrate samples sent to the Haemophilia Centre at the Churchill Hospital for aspirin resistance studies. They did not have any other study bloods taken.

3.5.3. Study blood at 1-month follow-up clinic

Study patients attending the clinic for 1-month follow-up had blood taken for aspirin resistance studies at the Haemophilia Centre. Two full citrate (blue) tubes were taken with the date and time of collection stated clearly on the red haematology card, together with the date and dose of the last aspirin taken prior to collection. Any other anti-platelet or anti-coagulation or statin medication was also recorded. The blood was tested within 4-6 hours after venepuncture. If patients who had not had aspirin resistance blood taken at their initial event, if they were subsequently admitted and were on aspirin further citrate samples were taken and sent for analysis at the Haemophilia Centre.

3.5.4. Study blood at 1-year follow-up clinic

Study patients attending the clinic for 1-year follow-up had blood taken for aspirin resistance. Two full blue tubes (1x 3.2 citrate and 1x 3.8 citrate) with details as above. Further serum and plasma samples were also taken. Clinical bloods for FBC, TSH, LFT U&Es and cholesterol were sent routinely for analysis.

3.5.5. Collection of acute blood samples from Biochemistry

Blood samples could be collected from Biochemistry if a fresh sample of blood was not collected from the patient within 48 hours of event. Acute serum and plasma were generally available for collection as these were only discarded routinely 7 days after collection. A list of samples required, including the patients name, hospital number and date of collection were handed in to biochemistry on Friday for collection on Monday. Patients were ascertained rapidly and this method of obtaining blood was not often necessary.

3.6. Procedure for further data collection of investigations

All patients were assigned a unique folder with an identification number. These folders held data collection forms, consent or assent, follow-up data and copies of results of relevant investigations. Copies of relevant information from the hospital or GP record were also obtained. This was relatively easy for patients attending the daily clinic were notes were easily accessible. For in-patients, notes were requested after the patient's discharge and the following information copied as indicated and incorporated into the patient's folder:

- Relevant history and examination.
- Correspondence regarding any vascular history.
- Blood results were printed off from the ORH intranet.
- Premorbid ECG if available and serial ECGs day 1-3.
- Radiology reports of CXR, brain imaging and carotid Doppler.
- Cardiac investigation results.

- Ankle-brachial pressure index results and Duplex results.
- Coronary, peripheral, carotid or cerebral angiography results.

3.7. Diagnosis and classification

To ensure accurate phenotyping and classification using TOAST criteria,[63] all TIA and stroke cases had a full clinical assessment, ECG, carotid Doppler and brain imaging. Echocardiography was carried out if clinically appropriate. CT and MRI brain imaging were formally reported and coded by the OCSP neuroradiologist (Appendix 17). If there was no brain imaging cases were classified using the Allen score for clinical differentiation between ischaemia and haemorrhage.[64] Post mortem reports were obtained and reviewed.

TIA and stroke cases were classified using the OCSP classification[65] and TOAST criteria[63] by two study physicians. Details of all potential strokes were reviewed regularly with Dr Rothwell (Neurologist), Professor Warlow and Dr Anslow (Neuroradiologist).

Clinical history, serial ECGs and cardiac enzymes of all suspected MI were reviewed at regular meetings with Dr Adrian Banning (Consultant Cardiologist). MI cases were classified clinically, epidemiologically using OXMIS criteria[62] and using the troponin based definition advocated by ESC/ACC criteria.[66]

Any diagnosis of critical limb ischaemia or acute peripheral vascular events was confirmed by the Consultant Vascular Surgeon caring for the patient.

3.8. Follow-up

Follow-up of patients presenting with acute events was coordinated with the Department of Primary Care (Professor D Mant and colleagues). Follow-up assessed clinical, functional and psychological outcomes, documented health services use, and identified reasons for failure to utilise effective strategies for secondary prevention.

The follow-up strategy (Appendix 18) depended on the nature of the incident event. All patients were contacted at 1, 3, 6, and 12 months from incident event either by telephone or personal contact. ACS and PVE patients were followed up in collaboration with the Department of Primary Care by a Research Nurse. All TIA and stroke patients attending the daily clinic were seen at 1 and 12 months in a follow-up clinic at the Radcliffe Infirmary (Appendix 19) by Research Nurses. A physiotherapist saw patients at home at 3 and 6 months as part of her own *D Phil* research project into TIA and stroke recovery. Hospitalised TIA or stroke patients were invited to our 1 and 12 month follow-up clinic at the Radcliffe Infirmary and were seen at 3 and 6 months by the physiotherapist or research nurses in the patients own home. At follow-up patients were screened for recurrent events (Appendix 20). Any patient considered to have a recurrent event was reassessed by a study physician. All patients were interviewed on treatment concordance and health resource usage. Cognition was retested using MMSE. The Rivermead Mobility Index[67] was administered focussing intentionally on disability not impairment. This index focuses on fundamental activities such as walking or going up stairs. It is simple to use and reasonably reliable and valid.[67] The Nottingham Extended ADL index[68] was also administered. This is a 22-item interviewer administered questionnaire covering mobility, kitchen and other domestic tasks and leisure activities. Respondents have their level of activity assessed rather than their capability. The Hamilton Anxiety Depression Scale[69] was also applied to TIA and stroke cases. It has the advantage that it does not contain any somatic items that could reflect physical rather than psychological morbidity. This has been used previously in stroke patients.[70] These measurements will allow the study of stroke recovery comparing adaptation to disability versus true motor recovery.

The timing of follow-up related to the date of the incident event that led to notification. In the case of patients with ACS and PVE the date of ascertainment was often close to the date of the incident event. However owing to the multiple

overlapping sources of ascertainment there were occasions where ascertainment was delayed. In these circumstances follow-up at 1, 3, or 6 months were missed.

In circumstances where different acute vascular events occurred close together in time the follow-up schedule of TIA and stroke patients took priority, then ACS then PVE. Patients undergoing vascular interventions were not followed-up. However acute vascular events occurring in these patients were picked up through normal ascertainment protocols.

Any recurrence leading to hospital admission led to ascertainment through normal hot pursuit. A study physician reassessed recurrent strokes. To avoid duplication of data, if a patient had a recurrent vascular event in a different vascular territory within 1 year of the incident event a detailed recurrent event form was completed. Major changes in risk factors and drug history were noted. If such a recurrence was over a year from the incident event a new data collection form was completed. If a recurrence in the same vascular territory occurred only a recurrent form was completed whatever the time period.

In the second year of the study follow-up was scaled down and became more unified owing to changes in skill mix of the staff in the unit. Follow-up of all acute vascular events became the responsibility of the Stroke Prevention Research Unit. From 1st April 2003, all TIA, stroke, ACS and PVE patients were followed up at 1, 6 and 12 months with yearly telephone follow up thereafter. TIA and stroke patients were seen at all time points. ACS and PVE patients were seen at home at 1 and 12 months with a telephone follow-up at 6 months. This work was carried out by research nurses and a physiotherapist. Recurrent events, blood pressure, Barthel and Rankin were all collected and information was fed back to GP practices.

3.9. Pre-morbid risk factors

All patients included in OXVASC had premorbid data collected on pre-existing risk factors. These data were collected from GP records if available by research nurses. Data collection was facilitated by the increased computerisation of this information in most of the study practices. However written GP records were also scrutinised to identify premorbid risk factors such as measured blood pressures and cholesterols (Appendix 21). If patients died prior to ascertainment the patient record was requested from the Family Health Strategic Authority and subsequently reviewed. A GP encounter or summary form was obtained for all study participants. It is envisaged that all previous blood investigations will be made available from the Department of Biochemistry for patients registered in OXVASC.

3.10. Conclusions

The OXVASC study is the first population-based study of the incidence, case-fatality and long term sequelae of all atherosclerotic events in the same population at the same time. It will provide a wealth of high quality data for future analysis.

This population-based incidence study was not possible without the active participation of GPs and other primary care staff. All of the study practices were active collaborators. This confirms experience from OCSP[71] and OXMIS[62] that high quality population-based research is feasible in Oxford.

Multiple overlapping methods of ascertainment achieved accurate and complete identification of all acute vascular events in our population-based study (See chapter 5). However there were several cases that occurred while the patient was an inpatient for another indication. These patients would have already been excluded on the basis of the initial reason for their admission and would not routinely be subsequently reviewed. If they suffered a MI, it would be likely we would identify them from their troponin measurement. If they had a stroke, there were many other potential methods these events would have been ascertained including hospital

coding, subsequently GP referral or found on brain imaging or GP searches. None of these search strategies were fully effective and it is possible a small number were not ascertained. In addition we were heavily reliant on our collaborating GP practices to inform us of TIA and stroke cases that may have occurred and been investigated out of area. Myocardial infarction managed elsewhere were often identified through the GP searches.

Assessment of time trends of stroke incidence was possible as the OXVASC definitions were comparable with OCSP[70] (See chapter 9). This was faciltated by regular discussion with the OCSP principal investigator and all imaging reviewed by the OCSP neuroradiologist.

Comparison was much more difficult with respect to MI as troponin I measurement has become the routinely measured marker of cardiac necrosis in ORH and measurement of standard cardiac enzymes such as creatinine kinase (CK) and aspartate transaminase (AST) were no longer routine (See chapter 2). Standard cardiac enzymes were requested in a proportion of patients with abnormally raised troponin I to determine the impact of troponin I on the measured incidence of myocardial infarction.

The detailed data collected will provide a measure of the burden of vascular disease on a population-based level (See chapter 10) and will provide welcome up to date data that will guide funding for provision of clinical services.

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Chapter 4

The effect of case definition on measured stroke incidence

4.1. Introduction

Epidemiological studies are essential in order to measure the burden of stroke and to accurately guide clinical priorities, resource provision, and help target further research funding. A pre-requisite for comparing measured stroke incidence between studies is identical case definition in population-based, high-quality studies satisfying the Malmgren criteria.[1-11] Variation in case definition may have important effects on measured incidence rates.

Most stroke incidence studies have used the World Health Organisation (WHO) case definition.[12] This was developed in meetings held in 1971,[13,14] from which the WHO Stroke Register protocol was developed.[15] Cerebrovascular diseases were initially defined as diseases of the brain and spinal cord of a vascular origin,[13] but the definition of 'stroke' was limited to the clinical syndrome of 'rapidly developing clinical signs of focal or global disturbance of *cerebral* function leading to death or lasting more than 24 hours with no apparent cause other than a vascular one'.[12,13] This excluded transient cerebral ischaemia, systemic circulatory failure, hypertensive encephalopathy, chronic brain conditions with mental deterioration and gradually developing neurological abnormalities and cerebrovascular lesions discovered at autopsy that had not shown clinical manifestations in life.[14] 'By

convention,' this definition has excluded subdural, extradural or intracerebral haemorrhage caused by trauma, infection or tumour, and retinal infarction.[16]

In 1990, the WHO MONICA manual[17] listed definite focal signs suggestive of a stroke. It catalogued specific symptoms not acceptable as sole evidence of focal dysfunction such as localised headache, dysarthria and vertigo. 'Stroke events' in the context of blood disease (e.g. leukaemia, polycythaemia vera), or brain tumour and stroke caused by trauma were also excluded.[18-19]

In the same year the National Institute of Neurological Disorders and Stroke (NINDS)[20] published their case definition of stroke. Some groups[21-22] have used this and one group has presented its results using both WHO and NINDS definitions.[3,22] Stroke was used as a generic term including infarction, haemorrhage or subarachnoid haemorrhage (SAH). This included all disorders in which there was an area of brain permanently affected by ischaemia or bleeding and / or in which one or more blood vessels of the brain were primarily impaired by a pathological process. It noted brain haemorrhage was predisposed to by blood dyscrasia and anticoagulants but excluded traumatic associated intracranial haemorrhage.[20]

There are subtle differences between the commonly used stroke definitions that can be open to interpretation. For example the WHO definition[12,17] would imply that SAH with headache and meningism and no focal neurological disturbance should be excluded. In practice, most include these cases. Secondly, stroke is increasingly recognised as a highly heterogeneous disorder and there are a number of conditions that could now be considered to satisfy inclusion in a stroke (Table 4.1) incidence study. Other cerebrovascular syndromes might also be considered to reflect the burden of acute cerebrovascular events (Table 4.2).

Table 4.1. Conditions that might be considered as stroke

1. Retinal infarction
2. Venous infarction
3. Spinal infarction
4. Syndrome without focal neurological symptoms but an appropriate vascular cause on cranial imaging (e.g. intracranial haemorrhage with headache only but no focal symptoms or signs).
5. Migraine with neurological symptoms lasting more than 7 days without infarction on radiographic imaging.

Table 4.2. Syndromes that might be considered to reflect the burden of acute cerebrovascular events

1. Stroke syndromes without a clear ictus (e.g. history suggestive of cerebrovascular disease but no clear acute event.
2. Persistent neurological symptoms such as isolated vertigo, diplopia, dysarthria or hemisensory symptoms with no appropriate lesion on brain imaging.
3. Sudden deterioration in patients with significant cognitive impairment.
4. Encephalopathic syndromes that are associated with cerebral infarction on brain imaging (e.g. cerebral vasculitis, post-partum angiopathy).
5. Sudden death certified as stroke without post mortem.
6. Diffuse hypoxic brain injury or diffuse ischaemic brain injury without focal infarction (eg. post CABG).
7. Iatrogenic stroke in coronary or peripheral vascular intervention (e.g. during or post coronary angiography).
8. Isolated cranial nerve palsies of presumed ischaemic aetiology.
9. Non-traumatic subdural haematoma with focal neurological symptoms or signs.
10. Cerebral venous thrombosis without cerebral infarction.

We have determined the effect of different inclusion criteria on measured stroke incidence rates using the Oxford Vascular (OXVASC) Study. This is a large prospective population based study of all acute vascular events including the active pursuit of all suspected cerebrovascular events.

4.2. Methods

In the first year of OXVASC all potential acute cerebrovascular events were identified using hot and cold pursuit with multiple overlapping sources of ascertainment.[23] The study population comprised all patients who were fully

registered with 63 General Practitioners (FPs) based in 9 family health centres. These collaborating practices routinely referred patients to the Oxford Hospitals, had accurate computerised age-sex registers (ASR) and were willing to refer any patient with a suspected acute cerebrovascular event. The population was made up of predominantly Caucasian (94%) as well as Asian (3.1%), Chinese (1.5%) and Afro-Caribbean (1.4%)[24] and 45% were over the age of 40.

Collaborating FPs were encouraged to refer any patient whom they thought may have had an episode of acute neurological dysfunction caused by cerebrovascular disease. Electronically generated hospital admission registers were reviewed daily. Patients admitted to the Medical Admissions Unit, Acute Stroke Unit, Neurology and Neurosurgical and Rehabilitation wards were identified on a daily basis. Causes of hospital deaths were recorded. Cases of retinal ischaemia referred to the Eye Hospital were reviewed. All referrals for brain and carotid imaging were identified and their notes reviewed. Monthly discharge coding data were provided for all patients with diagnoses coded to the International Classification of Diseases (10th Revision) (ICD-10) for cerebrovascular disease. The regional Department of Public Health provided a list of all patients with an ICD-10 vascular code cause of death on a quarterly basis. GP-databases were searched for all patients coded with a cerebrovascular diagnosis and all deaths occurring in the community were identified on regular visits to the practices. Patients were assessed as soon as possible after the event by a study clinician at home hospital or in a dedicated clinic. All available medical records were reviewed. Two study physicians discussed the cases and agreed on each diagnosis.

We have determined the burden of all potential acute cerebrovascular events and considered what might be included in a stroke incidence study depending on case definition. We have also examined the inclusion and exclusion criteria detailed in other published population-based studies. We have studied the effect of case definition on measured stroke incidence rates.

4.3. Results

In the first year of OXVASC, 1213 presumed vascular events were considered for inclusion in this study of all incident and recurrent acute vascular events and patients undergoing endovascular or vascular surgical procedures. There were 424 possible cerebrovascular syndromes of which 112 were assessed at the clinic and were felt not to have a cerebrovascular aetiology (Table 4.3). There were 107 transient cerebrovascular episodes. There were 205 patients with acute cerebrovascular events of which 161 were incident. 128 stroke syndromes were directly comparable with WHO[17] and OCSP.[2]

Table 4.4 describes all of the incident acute cerebrovascular events considered for study inclusion. Of the 34 possible strokes, 1 was recurrent. Many studies did not publish details on their inclusion and exclusion criteria with a few notable exceptions.[7,11,25] Others may have done the same but this was not published. A few reported cerebrovascular disorders such as diffuse brain injury, [6,7,11] sudden deterioration in cognition,[7,10,11] subdural haematoma,[4,7,10,11] and sudden death certified as stroke without autopsy,[21] that were subsequently excluded from their further analysis.

Table 4.3. Diagnoses of all incident and recurrent acute cerebrovascular events considered for inclusion in OXVASC

Diagnosis	Number (424)
Definite stroke	171
Possible stroke	34
TIA	87
Possible TIA	20
Other diagnosis (n=112)	
Migraine	25
Anxiety	14
Seizure	9
Peripheral neuropathy	8
Arrhythmia	6
Labyrinthine	6
Postural hypotension	6
Transient global amnesia	6
Syncope	5
Tumour or metastases	4
Cervical spine disease	3
Dementia	2
Myasthenia gravis	1
Multiple sclerosis	1
Parkinson's disease	1
Other not specified (General medical, vasovagal, anaemia, hypoglycaemia etc)	15

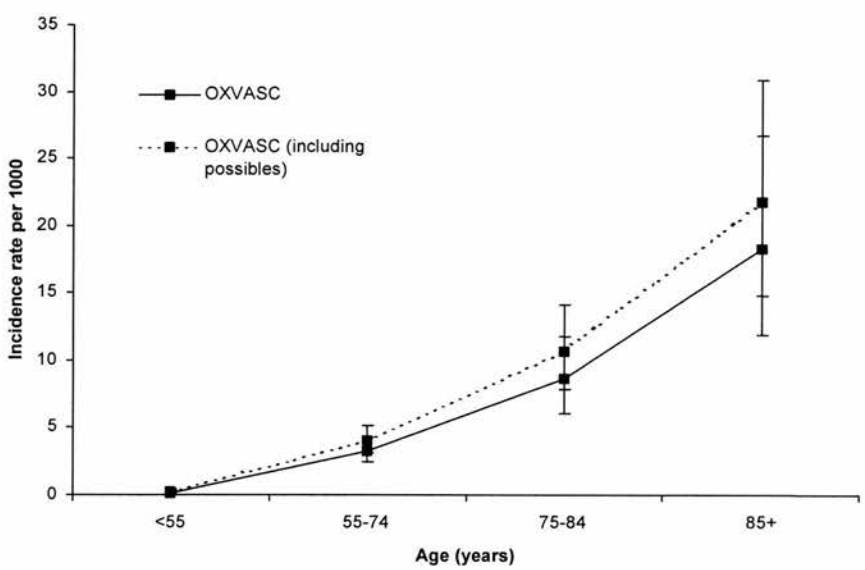
Table 4.4. Possible stroke-like syndromes ascertained in OXVASC and the reporting of these syndromes in other studies

Diagnosis (Number in OXVASC)	No. of studies not reporting if diagnosis included	No. of studies excluding diagnosis [Ref]
Retinal infarction (4)	11	2 [7,11]
Venous infarction (1)	13	0
Spinal infarction (1)	13	0
Diffuse brain injury (5)	10	3 [6,7,11]
No focal deficit (1)	13	0
Migrainous stroke (1)	11	2[7,11]
Stroke without clear Ictus (3)	11	2[7,11]
Isolated vertigo, diplopia, dysarthria or hemisensory symptoms (3)	11	2[7,11]
Sudden deterioration in patients with significant cognitive impairment (3)	10	3 [7,10,11]
Encephalopathic Syndromes (0)	12	1[11]
Isolated cranial nerve palsies of presumed ischaemic aetiology (4)	13	0
Subdural haematoma (4)	9	3 [4,7,10,11]
Cerebral venous Thrombosis without cerebral infarction (1)	13	0
Sudden death certified as stroke without autopsy (2)	12	1[21]

In OXVASC there were 4 cases each of retinal infarction, 4 cases of presumed ischaemic cranial nerve palsies, and 3 cases of sudden cognitive deterioration in patients with pre-existing dementia without any other identifiable cause. There were one case each of venous and spinal infarction and migrainous stroke. Several other syndromes could not be ascribed to a non-vascular cause. There were also 2 patients had been certified as strokes that had died suddenly without any positive features of a stroke diagnosis (Table 4.4).

The adjusted overall annual stroke incidence rates per 1000 England and Wales population using the standard WHO definition[17] was 1.6 (95%CI, 1.32-1.88). If all other possible stroke syndromes were included the adjusted rate was 2.01 (95%CI, 1.70-2.32) / 1000 population (p = 0.05). (Figure 4.1)

Figure 4.1. Age adjusted incidence rates per 1000 population for all definte and possible strokes vs OCSP defined strokes



4.4. Discussion

To ensure comparability between different stroke incidence studies there needs to be similar case definitions. Heterogeneous stroke syndromes have been increasingly recognised with better brain imaging, but it is uncertain whether some of these have been included in published 'ideal' stroke incidence studies. We have shown that the burden of incident acute cerebrovascular events may vary by 20% depending on case definition.

Certain stroke syndromes are worthy of consideration for inclusion or documentation in future incidence studies. It is likely that some of these have not been included purely as they may present to other specialities. For example retinal infarction has been included as an outcome in an intervention study[26] but has not been included in incidence studies. Venous stroke has been increasingly recognised as a cause of haemorrhagic infarction. Spinal infarction has traditionally been excluded because of its location. Migrainous strokes were included in OCSP[2] but it is uncertain whether cases were included in other incidence studies and it is not clear whether migraine with prolonged neurological deficit without infarction on cranial imaging should be included in incidence studies.

Although the WHO definition is the broadly accepted standard, there remain uncertainties. Firstly, it would imply that subarachnoid haemorrhage (SAH) with sudden onset headache, meningism and no focal or global disturbance of cerebral function should be excluded. However, in practice most investigators include all SAH cases. Secondly, with improved brain imaging, the diagnosis of small intracerebral haemorrhage in patients with lone headache is increasingly recognised and it is not clear whether this should be included. One of our cases was a 70 year old man who had thrombolysis for a myocardial infarction. Several days later he complained of a localised headache with no other focal neurological disturbance. CT showed a small lobar haemorrhage. Thirdly, none of our subdural cases were

associated with trauma but all had focal neurology. Their brain imaging led to their exclusion.

Both the Perth[7] and Melbourne[11] groups described their exclusion criteria in detail and the Rochester group[25] clearly defined their inclusion criteria. The latter included non-haemorrhagic infarction secondary to vasculitis or haematological disease but excluded intracranial haemorrhage in the setting of haematological abnormality, encephalitis or tumour. SAH occurring in the presence of a haematological disturbance was excluded if no arteriovenous malformation or aneurysm was found. The WHO MONICA register[17] also excludes stroke events (implying both cerebral infarction and haemorrhages) in cases of blood disease but the NINDS definition[20] lists blood dyscrasia as a predisposing factor to brain haemorrhage in its classification of stroke types.

There are clinical syndromes that should continue not to be included in incidence studies. For example, patients with diffuse ischaemic brain injury without focal infarction after interventions such as coronary artery bypass grafting or cases where there is no clear ictus but may have relevant evidence of ischaemic damage on cranial imaging. Patients with acute hemisensory symptoms and no signs of infarction on cranial imaging reflect a difficult diagnostic group. Those presenting with sudden confusion are commonly labelled as TIA or stroke, and in those with significant pre-existing cognitive impairment, neurological assessment is often difficult and a vascular cause to the deterioration may be difficult to rule out particularly if no other systemic cause is found. More research is required to clarify the burden of such events and the prognosis for these groups.

There is considerable variation in the definition of fatal stroke cases. Most studies [2-11,19,21,,25] reviewed death certificates and autopsy reports. Several[6,9,10,25] specifically excluded patients certificated as stroke but who died within 24 hours of onset and had no clinical evidence of focal neurological deficit, no brain imaging and no

autopsy. The Novosibirsk study[21] excluded certificated cases of stroke if the period between onset of symptoms and death was less than 2 hours, there was no autopsy or no clinical record. However, this issue remains difficult clinically and epidemiologically. We identified an 83-year old lady admitted with an acute coronary syndrome and severe biventricular heart failure complicated by asystolic cardiac arrest. Her autopsy showed signs of severe heart failure with large bilateral pleural effusions and hepatic engorgement. However, there was also an acute parietal haemorrhagic infarction. A fairly consistent decline in stroke mortality has been reported[27] that has stabilised more recently.[28] However, secular trends in stroke types based on routine mortality data are strongly affected by changes in diagnostic fashion.[29] For ideal incidence studies, a positive diagnosis of stroke either clinically before death, on brain imaging or autopsy should be a obligatory.

In conclusion, we have described the type of acute cerebrovascular events identified in a well-designed population-based study fulfilling the criteria for an ideal incidence study.[1] There are potential difficulties in the interpretation of the commonly used stroke definitions and the impact of different interpretation is unclear. In many studies, there is a lack of published detail on inclusion and exclusion criteria. There are a number of syndromes including retinal, venous and spinal infarction that should be considered for inclusion or at least documented if possible. Finally there needs to be clarity as to which stroke events should be included in the context of haematological disease.

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Chapter 5

Direct assessment of completeness of ascertainment in a stroke incidence study

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5.1. Abstract

Background: Validity of comparisons of stroke incidence between studies or time periods depends on the completeness of ascertainment. Ascertainment cannot be reliably assessed indirectly by statistical methods, such as capture-recapture. We report the first use of direct methods to determine the completeness of different ascertainment strategies in a population-based stroke incidence study (Oxford Vascular Study).

Methods: We assessed completeness of two different ascertainment strategies: the *core* methods common to most previous incidence studies; and *core* plus *supplementary* methods used in some studies (including access to carotid and brain imaging referrals and assessment of patients referred as "TIA" or "recurrent stroke"). We assessed completeness of ascertainment in two ways. First, we searched anonymised primary care electronic patient records of the whole study population (n=90,542). Second, we interviewed and followed-up a high-risk subset of our study population: all patients who had an acute coronary or peripheral vascular event or a related elective investigation or intervention.

Results: 126 strokes were ascertained by the *core* plus *supplementary* methods, of which only 108 were identified by the *core* methods alone. Only two additional

incident strokes were identified by access to primary care electronic patient records of the whole study population. Assessment and follow-up of 1103 high risk individuals (5.5% of our total study population aged over 60 years) identified 16 incident strokes. However, all 16 had already been ascertained by the *core* plus *supplementary* methods.

Conclusions: The *core* methods of ascertainment used in some stroke incidence studies lead to significant under-ascertainment. However, direct assessment of ascertainment suggests that the *supplementary* methods used in recent studies can lead to near-complete ascertainment.

5.2. Introduction

Comparing stroke incidence between studies and measuring changes in incidence over time requires studies to use the same case definitions and methods of ascertainment.[1] However, there are few published data on the effect of different methods and intensity of ascertainment on measured incidence rates. Several stroke and/or transient ischaemic attack (TIA) incidence studies[2-20] have fulfilled the methodological criteria published by Malmgren et al[22] and refined by Sudlow and Warlow,[23] but there is still considerable variation in methods of ascertainment between these studies (Table 5.1). Some differences will be related to the organization of health care in the particular country or area, but others are more generic. For example, the studies in Table 5.1 differed in relation to whether patients referred as "TIA" or "recurrent stroke" were reviewed, and only half used carotid and brain imaging referrals as a method of ascertainment. These supplementary search strategies may have important effects on ascertainment and hence measured incidence rates.

Assessment of the completeness of ascertainment is very difficult. Several indirect statistical modelling methods, including capture-recapture,[24] have been proposed, but these are poorly validated and are based on several assumptions the validity of

which is often uncertain.[25-29] Indeed, capture-recapture models have frequently been shown to be unreliable in situations where these assumptions do not hold.[27-29] For example, when sources are dependent,[30] or some sources have a very low probability of capture,[31] capture-recapture methods are inapplicable. It is possible to allow for the violation of these assumptions using covariates, but when some categories have small numbers, the resulting estimates are unstable.[32]

Table 5.1. Use of supplementary methods of ascertainment in recent 'ideal' stroke incidence studies

	TIAs Assessed Reviewed	TIAs followed up	Recurrent strokes assessed	Carotid & brain scan referrals
OXVASC (2002-)[21]	Y	Y	Y	Y
OCSP (1981-86)[2,3]	Y	Y	N	N
Dijon (1985/1994)[4]	Y	Y	Y	N
Rochester (1985-89)[5]	Y	N	Y	N
Umbria (1986-89)[6]	Y	Y	Y	N
Valle D'Asto (1989)[7]	Y	N	Y	Y
Fredericksburg[8] (1989-90)	N	N	Y	N
Perth (1989/1995)[9,10]	Y	Y	Y	Y
Warsaw (1991-92)[11]	N	N	Y	N
Auckland (1991)[12]	N	N	Y	Y
Novosibirsk (1992)[13]	Y	N	Y	Y
Erlangen (1994-98)[14]	Y	N	N	N
Greece (1993-95)[15]	N	N	N	N
Melbourne (1996)[16]	Y	N	Y	Y
L' Aquila (1994-98)[17]	Y	N	Y	Y

Direct assessment of the completeness of ascertainment is time-consuming and expensive, and has not previously been attempted in a stroke incidence study, but is likely to be more reliable. We used two direct methods to estimate potential under-ascertainment in the Oxford Vascular Study (OXVASC). First, to identify non-ascertained patients who had presented to medical attention but had not been notified to the study, we accessed anonymised primary care electronic patient records of all of our study population. Second, to estimate the number of individuals who had had a stroke but were not ascertained because they had not been notified to the study or had not presented to medical attention after their stroke, we interviewed and followed-up a subset of our population which we considered to be at high risk of stroke: all patients who had an acute coronary or peripheral vascular event or a related elective investigation or intervention.

5.3. Methods

Study Population: The population (mid-year n=90,542) comprised all patients who were fully registered with 63 Family Physicians (FP) in nine primary health care centres in Oxfordshire, UK. In the UK, patients register with a FP who provides their primary health care and, when necessary, refers them to secondary care. The FP receives all relevant information about specialist consultations, emergency department attendance and hospital admissions even if these do not occur locally. Thus, the FP holds a lifelong record of all medical events as well as details of each consultation with the FP. This individual record is transferred to a new FP if the patient moves residence. The collaborating FP practices were chosen if they were in Oxfordshire routinely referring patients to the Oxford Hospitals, had an accurate computerised age-sex register (ASR), were willing to refer any patient with a suspected acute cerebrovascular event, and were computerised, allowing searches for cerebrovascular diagnostic codes. The ASR provided accurate and up-to-date estimates of the denominator allowing easy identification of cross boundary flow and turnover within the population. The population was 94% Caucasian, 3.1% Asian, 1.5% Chinese, and 1.4% Afro-Caribbean.[33]

Case Ascertainment: We attempted to ascertain all incident or recurrent strokes and TIAs occurring between 01/04/02 and 31/03/03. Ascertainment continued for 3 months until 30/06/03 for patients presenting late with a TIA or stroke that had occurred on or before 31/03/03. Case ascertainment included patients who had an event whilst temporarily away from Oxford, but not visitors to Oxford who were not normally resident or registered with a FP. A liaison FP in each practice checked with colleagues regularly to ensure that all relevant patients were referred, and a study nurse visited each practice monthly. A quarterly newsletter was sent to all FPs. The study was approved by the Oxfordshire Research Ethics Committee.

Multiple overlapping sources of case ascertainment were used to identify potential patients using hot and cold pursuit. These are listed below as either *core* methods, common to most previous incidence studies that satisfy the Malmgren criteria (table 5.1), and *supplementary* methods, used in some previous studies.

Core methods of case ascertainment:

Hot pursuit

- FP referral of all possible acute cerebrovascular events to daily TIA and stroke clinic.
- Daily review of computer-generated Hospital and Emergency Department admission registers.
- Daily review of acute medical wards and case note review.
- Daily review of all case notes of patients dying in hospital.

Cold pursuit:

- Weekly review of case notes of patients attending clinics of other local physicians.
- Monthly contact with Paediatrics, Obstetrics and other relevant departments to identify stroke cases.
- Monthly review of hospital diagnostic coding data.

- Monthly visit to Coroners office and review of post mortem results.
- Monthly visits to FP practices with regular contact with liaison FP.
- Quarterly review of Department of Public Health generated mortality file of all ICD-10 (I64) stroke deaths.

Supplementary methods of case ascertainment:

- Ascertainment of all patients referred as "TIAs".
- Follow-up of all patients with incident or recurrent TIA.
- Ascertainment of all cases referred as "recurrent strokes".
- Review of all referrals for brain, carotid or cerebral vascular imaging.

Clinical assessment, investigation and case definition

The patients were assessed as soon as possible after the event by a study clinician in a daily stroke and TIA clinic, in hospital or at home. We attempted to obtain a CT brain scan in every case. Informed consent was sought if possible. Otherwise, relatives were contacted to obtain assent. If a patient died prior to assessment, we attempted to obtain an eyewitness account from a relative as well as reviewing information in FP and hospital notes. For patients with sudden death the post mortem result was reviewed.

The WHO definition of stroke[34] was used: rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and to those with subarachnoid haemorrhage), loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. A TIA was defined as an acute loss of focal cerebral or ocular function with symptoms lasting less than 24 hours and which after adequate investigation was presumed to be embolic or thrombotic vascular disease.[35]

Direct assessment of under-ascertainment

We used two direct methods to assess under-ascertainment of stroke. First, to detect under-ascertainment of patients who had presented to medical attention, we searched anonymised electronic patient records of all of our study population in each of the FP practices. Any patients with a diagnostic code related to cerebrovascular disease were identified. If they were not already known to the study, they were contacted after obtaining permission from the FP, and assessed.

Second, to determine under-ascertainment due possibly to patients not presenting to medical attention after their stroke, we interviewed a subset of our population who we considered to be at high risk of stroke. Using similar overlapping hospital and community-based methods of case-ascertainment to those described above for TIA and stroke, we attempted to identify all patients in our study population presenting during the study period or the next six months with an acute coronary syndrome (myocardial infarction or unstable angina) or an acute peripheral vascular event (peripheral thromboembolism or critical limb ischaemia, aortic aneurysm etc), or a related elective investigation (e.g. exercise testing and coronary or peripheral angiography) or intervention (e.g. coronary, aortic or peripheral angioplasty/surgery). All of these patients were interviewed by a study physician and asked about previous diagnoses of TIA or stroke and about neurological symptoms that might be suggestive of TIA or stroke during the study period. Their hospital and FP medical records were also reviewed. All patients were also followed-up for the duration of the study period by face to face interview with a study nurse at 1, 3, 6 and 12 months after the event/intervention.

Analysis

All strokes were categorised as incident ("first-ever-in-a-lifetime") or recurrent. All analyses of ascertainment were confined to incident strokes. We determined the effect of *core* versus *core* plus *supplementary* methods of ascertainment on the completeness and speed of ascertainment of incident strokes. We cross-referenced

all strokes that were ascertained by the direct methods of assessment of completeness with those identified by the *core* plus *supplementary* methods.

5.4. Results

A total of 128 incident strokes were identified by all methods of ascertainment, including the direct methods of assessment of completeness, 115 (90%) of which were assessed by a study physician. Twelve patients died prior to being seen and one had their event whilst abroad, was fully investigated, but refused further follow-up. 117 (91%) were ascertained by hot pursuit. 73 (57%) were hospitalised.

126 (98%) incident strokes were identified by the *core* plus *supplementary* methods of ascertainment, but only 108 (84%) were identified by the *core* methods alone. 18 (14%) patients were referred by their GP as "TIA" but were found on assessment to be minor strokes, of which 16 would not have been identified by *core* methods alone. All of these patients were also identified from referrals for brain and carotid imaging. Assessing all patients who were referred as "recurrent" strokes did not identify any first-ever-in-a-lifetime strokes. Follow-up of 118 incident and recurrent TIAs identified six incident strokes during the study period, all of which had also been ascertained by *core* plus *supplementary* methods.

Using the *core* plus *supplementary* methods of case ascertainment, 5 incident strokes were identified from only one source, whereas 41 cases had only one source of ascertainment by core methods alone (table 5.2), of which 28 (71.8%) were identified only through referral by our collaborating FPs. For 18 incident strokes the *supplementary* methods of ascertainment were the first source and lead to earlier clinical assessment than would have been the case if ascertainment had depended on the *core* methods alone.

Table 5.2. The effect of the use of different search strategies on the number of overlapping sources of ascertainment

	Core methods only n = 108	*Core* and *supplementary* methods n = 126
One source only	41	5
>= 2 sources	34	37
>= 3 sources	26	48
>=4 sources	6	28
>= 5 sources	1	4
>= 6 sources	0	4

Direct assessment of under-ascertainment

The direct tests of completeness of ascertainment identified only two incident strokes that had not been ascertained by *core* plus *supplementary* methods. Access to primary care electronic patient records of the whole study population identified 252 patients with a diagnostic code for cerebrovascular disease during the study period, of which 162 were possible strokes. Further investigations of these cases identified 113 incident strokes, of which only two had not been otherwise ascertained. One was a 66 year-old man who had a stroke while visiting the USA, where he was fully investigated and had not wanted any further assessment on his return to the UK. The other case was an 81 year-old woman who had a minor ischaemic stroke following gynaecological surgery, which was not identified on hospital discharge coding, but which was reported to her FP.

In addition, we assessed and followed up 1103 individuals who had a total of 1676 non-cerebral vascular events, investigations or interventions during the study period or the subsequent six months. The majority (78%) of these individuals were over 60 years of age, and comprised 5.5% of our total study population in this age range. 146 of these individuals presented with a rapidly fatal vascular event and could not therefore be questioned or examined. However, the hospital and FP records of all of these individuals were reviewed. 39 patients refused to consent to questioning or examination and a further 20 refused to consent to follow-up, and all but 5 of these individuals allowed us to review their hospital and FP records.

As expected these patients did represent a high-risk group. We found 16 patients who had had an incident stroke during the study period, giving a crude incidence of nearly 15 per 1000, which was approximately double the age/sex adjusted rate expected from the incidence rate of the study population as a whole. However, all of these incident strokes had been ascertained by the *core* plus *supplementary* methods. Moreover, we found no patients with a clinical history or signs suggestive of a stroke during the study period who had not presented to medical attention.

5.5. Discussion

The Malmgren criteria[2] for "ideal" stroke incidence studies were published 17 years ago and may no longer reflect current practice. Those studies that have satisfied the criteria have used a commonly accepted set of multiple overlapping sources of ascertainment, including collaboration with FPs, that we have termed the *core* methods. There is usually direct collaboration with primary care physicians, although the large population covered by the Auckland study[12] meant that contact was only possible with a random subset of FPs, and the Rochester study[5] used the unique Epidemiological Project Medical Record Linkage System, which includes primary care. However, additional methods of ascertainment have been used in some studies. Several studies assessed patients referred as TIA in addition to strokes, [3-7,9,10,12,14] and some of these studies also followed-up patients with TIA.[2-4,6,9,10,21] Several studies also assessed "recurrent" strokes,[4-13,16,21] and about half reviewed all requests for carotid and brain imaging. [7,9,10,12,13,16,17,21] Since all of these *supplementary* methods were used in OXVASC, we were able to assess their usefulness in comparison with the *core* methods alone.

We found that the *core* methods alone failed to ascertain 15% of incident strokes. Nearly all of these strokes were, however, identified by the *supplementary* methods. Assessment of patients referred as TIAs and reviewing brain and carotid imaging referrals were particularly important sources of additional cases and should probably become the norm in planning future 'ideal' stroke incidence studies. These supplementary methods also allowed more rapid ascertainment and hence earlier clinical assessment, which is important in terms of accurate diagnosis and clinical phenotyping.

The most novel aspect of our study was the attempt to directly assess the likely completeness of ascertainment. We were fortunate to have access to the anonymised electronic medical records of our whole study population. Although,

this source did not identify all incident strokes, 90% (113/126) of incident strokes that we identified by our *core* plus *supplementary* methods of ascertainment were recorded on the electronic FP patient record showing that the recording of diagnoses by FPs was reasonably efficient. It is reassuring, therefore, that only two additional strokes were identified by this method that had not been ascertained by our *core* plus *supplementary* methods.

We also assessed completeness of ascertainment by interview and follow-up of all patients in our study population presenting during the study period or the next six months with an acute coronary syndrome (myocardial infarction or unstable angina) or an acute peripheral vascular event (peripheral thromboembolism or critical limb ischaemia, aortic aneurysm etc), or a related elective investigation (e.g. exercise testing and coronary or peripheral angiography) or intervention (e.g. coronary, aortic or peripheral angioplasty/surgery). Virtually all of these patients were interviewed and examined by a study physician, and their hospital and FP medical records were assessed, or they agreed to review of their records, and the vast majority consented to be followed-up regularly by face-to-face interview. Although this group included 5.5% of our total study population aged over 60 years and had a high incidence of stroke, we did not identify any individuals with incident stroke who were not ascertained by our *core* plus *supplementary* methods or any individuals who had not presented to medical attention after an incident stroke during the study period. It is highly likely that we did miss some incident strokes in the remainder of our study population, but our findings in the high-risk subset suggest that ascertainment was very close to complete.

Potential shortcomings

Although we believe that our results are internally valid, the main shortcoming of studies of methods of ascertainment in stroke incidence studies is the potential difficulty in generalising the findings. There are likely to be subtle differences in the way in which the *core* and *supplementary* methods of ascertainment are used in

different studies and there are many differences between health care systems that could influence the effectiveness of particular methods of ascertainment. For example, in OXVASC we are fortunate to have a highly motivated group of collaborating FPs, many of whom were also involved in the previous Oxfordshire Community Stroke Project (OCSP).[2] Completeness of ascertainment by direct notification from FPs might be lower in studies with less collaborative colleagues in primary care or less cohesive health care systems. Similarly, health care systems differ in the proportion of patients with stroke, particularly minor stroke, who are admitted to hospital for investigation and treatment. This proportion varied from 54% to 95% in the studies listed in table 1. The relative utility of the different methods of ascertainment will therefore differ between studies. The method of assessment of potential stroke patients who are ascertained also differs.

Despite these differences between studies, we believe that some useful and generalisable conclusions can be drawn from our findings. Firstly, the *core* methods of ascertainment that are regarded as acceptable for an "ideal" incidence study should be supplemented where possible. For example, assessment of all referrals for brain and cerebrovascular imaging was a very useful source of ascertainment in OXVASC and should be possible in most studies. Similarly, assessment of patients referred to secondary care or recorded in primary care as having had a "TIA" identified several patients in OXVASC who had, in fact, had a minor stroke. Two other studies reported similar proportions of strokes that were initially referred as "TIA " (7% and14%).[3,9,10]

Secondly, our direct methods of assessment of completeness of ascertainment were time consuming and expensive but identified few additional incident strokes. We therefore conclude that if the same *core* and *supplementary* methods of ascertainment that were used in OXVASC are used in other stroke incidence studies in similar heath care systems, ascertainment is likely to be close to complete. The previous

Perth study[9,10] falls into this category, and with the exception of follow-up of patients with TIA, several other studies used comparable methods.[7,16,17]

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Chapter 6

Under-estimation of the early risk of recurrent stroke: evidence of the need for a standard definition

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6.1. Abstract

Background: There is considerable variation in the definitions used for recurrent stroke. Most epidemiological studies exclude events within the first 28 days (e.g. MONICA) or in the same territory as the presenting event within 21 days (e.g. most stroke incidence studies). However, recurrence is most common during this early period and these restrictive definitions could underestimate the benefits of early prevention.

Methods: We determined the 90-day risk of recurrence after incident ischaemic stroke in two population-based cohorts (Oxford Vascular Study – OXVASC; Oxfordshire Community Stroke Project - OCSP) with the three most common definitions: any stroke ≥24 hours after the incident event excluding early deterioration not due to a stroke (definition A); as above, but excluding any stroke within 21 days in the same territory as the incident event (definition B); and any stroke ≥28 days after the incident event (definition C).

Results: 657 patients had 93 recurrent strokes during 24 hours to 90 days after the incident event. The 90-day recurrence risks (95%CI) using definition A were 14.5%

(11.5-17.5) in OCSP and 18.3% (10.8-25.8) in OXVASC. The equivalent risks using definitions B and C were 8.3% (5.9-10.8) and 4.8% (2.8-6.7) respectively in OCSP and 7.0% (1.6-12.4) and 5.9% (1.0-10.9) in OXVASC. The definition A risk of recurrence was particularly high after partial anterior (22.9%, 17.5-28.2) and posterior (19.5%, 13.0-25.9) circulation strokes.

Conclusions: The three most widely used definitions of recurrent stroke yield markedly different 90-day risks. We suggest that, where possible, "definition A" be adopted as the standard to avoid underestimation of risk and to allow valid comparison of different studies.

6.2. Introduction

Approximately 30% of strokes in population-based studies are recurrent events, and these recurrent strokes are more likely than first strokes to be disabling or fatal. Prevention of recurrent stroke is therefore of considerable importance to both individual and public health. Reliable data are required on the absolute risk of recurrent stroke so that stroke prevention services can be organised appropriately and the likely cost-effectiveness of preventive treatments can be assessed. A standard definition of recurrent stroke is also required so that different studies can be compared or meta-analysed appropriately, time trends in risk can be determined accurately, and absolute risk reductions with treatment can be properly compared across trials.

The risk of stroke in the 3 months after a TIA is as much as 15-20% in population-based studies,[1, 2] whereas the equivalent risk after a first-ever ischaemic stroke is usually reported as 2-6%.[3-5] However, the majority of studies reporting these low risks excluded any potential recurrences that occurred within 21 days[6,7] or 28 days[8,9] after the incident stroke. The 28-day definition used in the MONICA study,[8] and other influential population-based studies,[9] excludes all strokes within 28 days, whereas other studies exclude only those events in the same vascular territory as the

original event.[10,11] The same distinction is made in studies which use the 21-day definition, either excluding all strokes within 21 days,[6,7] or only those strokes in the same vascular territory as the original stroke.[3,12,13] However, the distinction is relatively unimportant since most early recurrences are in the same territory as the initial stroke, particularly in patients with large artery atherosclerosis, in whom the risk of early recurrence is highest.[14] In contrast, other studies have used definitions that included all events occurring more than 24 hours after stroke, requiring only 24 hours of neurological stability prior to any recurrence,[14-16] and some appear to have also included new episodes occurring in a different vascular territory within 24 hours of the index stroke, either a new focal neurological deficit 'occurring at any time after the index stroke'[12] or an event that is 'clearly in another part of the brain after the preceding stroke'.[3,11,17] Finally, some studies have given no definition and relied on the clinical judgment of collaborating physicians,[18] or have not specified any time restriction.[19]

Given the importance of accurate determination of the risk of recurrent stroke, the potential for confusion due to the widespread use of very different definitions, and the possibility that some definitions underestimate the risk, we determined the effect of the most widely used definitions on the measured early risk of recurrent stroke in two high-quality population-based stroke incidence studies. Population-based data are necessary in order to minimise selection bias.

6.3. Methods

The methods of the Oxfordshire Community Stroke Project (OCSP) and the Oxford Vascular Study (OXVASC) are similar and have been described in detail elsewhere (see Chapter 2).[20,21] Both studies aimed to determine the incidence, risk factors and outcome of first-ever stroke in a prospective population-based study fulfilling the standard methodological criteria.[22] In OCSP (1981-1986), all patients in a population of 105,000 registered with 50 Family Physicians (FP) in ten practices in both urban and rural settings. The OXVASC population covered 90,542 registered with 63 FPs

from 9 practices, all of which had taken part in the OCSP. Each study developed multiple comprehensive overlapping search strategies to ensure as complete ascertainment as possible, and collaborated very closely with FPs, who were encouraged to report all patients with a suspected acute cerebrovascular event during the study periods. Collaborating practices provided an accurate age sex register with accurate and up-to-date estimates of the denominator allowing easy identification of cross boundary flow and turnover within the population.

In both studies, patients were assessed as soon as possible after the acute event by a study physician in a study clinic, in a hospital ward, or in the community. If a patient died prior to being seen, we attempted to obtain an eyewitness account as well as reviewing information with FP and in hospital or ambulance service notes. In addition to a detailed clinical assessment and routine blood tests, patients in both studies had CT brain imaging and all incident strokes were subtyped as ischaemic or haemorrhagic and according to the OCSP classification.[23]

In both studies, the date and time of onset of first stroke and the date and time of any acute neurological deterioration in the acute phase or suspected stroke during follow-up were recorded. In OXVASC all hospitalised patients were reviewed if any neurological deterioration was suspected. After discharge, or for patients who were not admitted to hospital, follow-up was of two kinds. Firstly, patients presenting to medical attention with a recurrent stroke would be re-ascertained by the same multiple overlapping search strategies as for incident strokes. Second, all patients were also reviewed face to face at 1, 6 and 12 months after the incident stroke by a research nurse. A study physician reassessed any patient in whom a recurrent vascular event was suspected and investigations, including brain imaging, were repeated.

A potential recurrent stroke was defined as any new acute neurological event with symptoms lasting longer than 24 hours occurring after the initial ictus of the

incident stroke (i.e. a definite acute worsening of an established non-progressive deficit) that was not attributable to oedema, brain shift, haemorrhagic transformation, intercurrent illness, hypoxia, seizures or drug toxicity. *Sudden* worsening was required for consideration as a potential recurrent event, and gradual progression of an acute deficit was excluded. Strokes occurring in patients who had a definite TIA (i.e. they returned entirely to normal within 24 hours) but had a subsequent stroke within 24 hours of onset of the TIA were also excluded.

Analysis

Based on the above criteria for a potential recurrent stroke, we applied the three most widely definitions of what constituted a recurrent stroke:

Definition A. Any recurrent stroke occurring more than 24 hours after the onset of the incident stroke, irrespective of vascular territory.[14-16]

Definition B. Any recurrent stroke occurring more than 24 hours after the onset of the incident stroke in a different vascular territory and any recurrent stroke occurring in the same territory more than 21 days after the incident stroke.[3,12,13] Territories were defined as left carotid, right carotid and posterior circulation. Note that previous users of this definition have varied in their interpretation. Most[3,12,13] stated that any recurrence within 21 days should be 'clearly in another part of the brain (eg contralateral hemisphere)'. Others classified all acute events occurring within 21 days as part of the same event.[6,7] In none of these reports is it clear whether strokes that occurred in other vascular territories within 24 hours of the incident stroke were included.

Definition C. Any recurrent stroke occurring more than 28 days after the incident stroke.[8,9]

Survival free of recurrent stroke was calculated from the time of onset of incident stroke by Kaplan-Meier analysis. Survival curves were produced for the definitions outlined above. The risk of recurrent stroke at 3 months was also determined for the different clinical subtypes.

6.4. Results

OXVASC enrolled 128 first-ever strokes, of whom 123 (96%) had brain imaging or post mortem. OCSP registered 675 first-ever strokes, of whom 542 (80%) had brain imaging or post-mortem. 13 OXVASC patients and 104 OCSP patients presented with primary intracerebral (PICH) or subarachnoid haemorrhage (SAH) and were excluded. A further 29 (5%) OCSP patients were excluded because of inadequate documentation of the course of the acute phase after the incident stroke. A total of 657 patients (OXVASC 115, OCSP 542) with a first-ever ischaemic stroke were therefore studied. The mean (SD) age and proportion of females were 75 (11.6) years and 54% (n=62) respectively in OXVASC and 73.2 (12.8) years and 50% (n=272) in OCSP. The vascular territories of incident strokes were carotid territory in 498 (75.8%; OXVASC 91, OCSP 407) and posterior circulation in 150 (22.8%; OXVASC 24, OCSP 126). Vascular territory was uncertain in 9 (1.4%) OCSP strokes. The OCSP classification of incident strokes was as follows: 154 (23.4%; OXVASC 28 (24.3%), OCSP 126 (23.2%)) lacunar infarcts (LACI); 230 (35.1%; OXVASC 49 (42.6%), OCSP 181 (33.4%)) partial anterior circulation infarcts (PACI), 152 (23.1%; OXVASC 25 (21.7%), OCSP 127 (23.4%)) posterior circulation infarcts (POCI); and 121 (18.4%; OXVASC 13 (11.3%), OCSP 108 (19.9%)) total anterior circulation infarcts (TACI).

The risks of recurrent stroke at 3 months based on the three different definitions were highly consistent across the two studies (table 6.1). If recurrence was confined to strokes occurring more than 28 days after the incident stroke (definition C), the 3-month risk was 4.8% (95%CI, 2.8 – 6.7) in OCSP and 5.9% (1.0 – 10.9) in OXVASC. The corresponding risks using the 21-day exclusion (definition B) were 8.3% (5.9 –

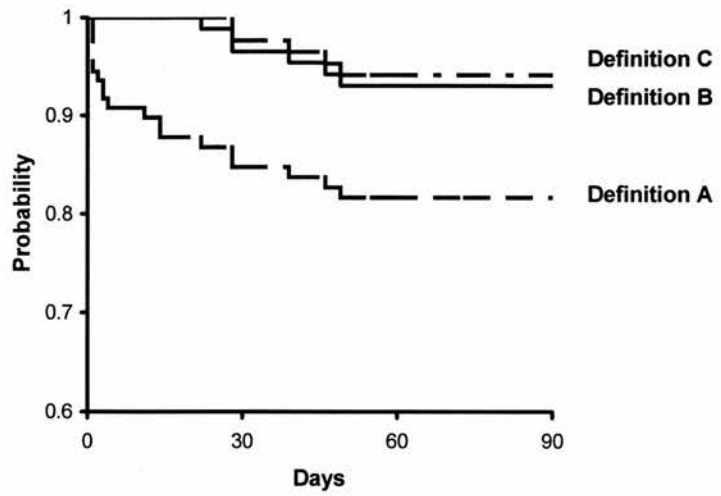
10.8) and 7.0% (1.6 – 12.4) respectively. In contrast, if only events within the first 24 hours after initial ictus were excluded (Definition A) the risks increased to 14.5% (11.5 – 17.5) and 18.3% (10.8 – 25.8) respectively. Figure 6.1 shows the Kaplan-Meier curves for survival free of stroke for each of the definitions of recurrence.

Table 6.1. The risk of recurrent stroke 3 months after a first-ever ischaemic stroke according to the three different definitions in two population-based studies (OXVASC and OCSP).

Definition	3 month % risk (95% CI)	
	OXVASC n=115	OCSP n=542
Definition A Any recurrence > 24 hours not attributable to oedema brain shift or haemorrhagic infarction.	18.3 (10.8 – 25.8)	14.5 (11.5 – 17.5)
Definition B Any recurrence > 21 days or if < 21 days new neurological deficit in different vascular territory.	7.0 (1.6 – 12.4)	8.3 (5.9 – 10.8)
Definition C Any recurrence > 28 days	5.9 (1.0 – 10.9)	4.8 (2.8 – 6.7)

Figure 6.1. Kaplan-Meier curves for survival free of stroke after a first-ever ischaemic stroke in OXVASC and OCSP for each of the definitions of recurrence.

OXVASC



OCSP

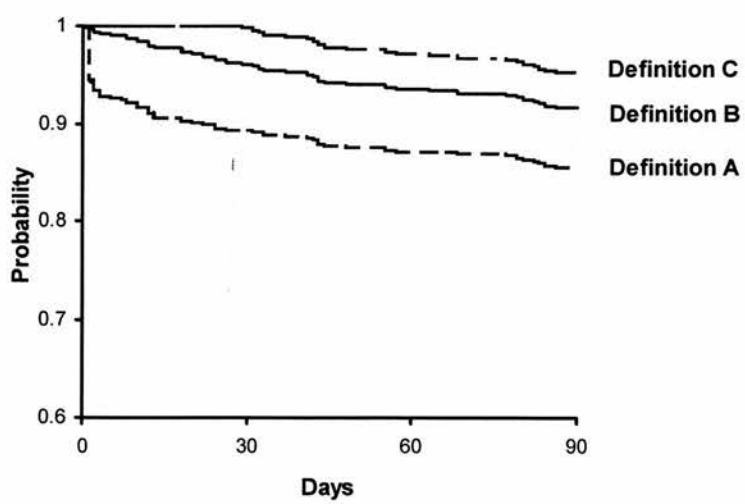
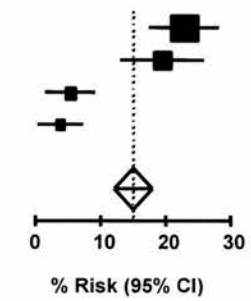
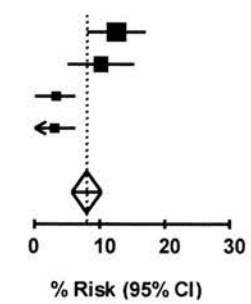


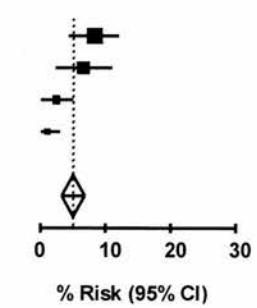
Figure 6.2 shows the 3-month risk of recurrent stroke according to the clinical subtype. There was no statistically significant heterogeneity in risks between OXVASC and OCSP for any subtype and the data from the two studies were therefore pooled. The difference in prognosis between the different subtypes was qualitatively similar with each definition, but was most clear cut for definition A. Patients presenting with a PACI and POCI were at highest risk of an early recurrence with each of the different definitions, the 3-month risk ranging from 8.1% (0.7-16.2) and 6.6% (2.2-11.0) respectively for definition C to 22.9% (17.5-28.2) and 19.5% (13.0-25.9) respectively with definition A. TACIs and LACIs had the lowest risk of early recurrence. These differences in risk were non-significant with definition C ($p=0.07$), moderately significant with definition B ($p=0.01$), but highly statistically significant with definition A ($p<0.0001$).

Figure 6.2. The 3 month risk of recurrent stroke according to OCSP clinical subtype[23] in OXVASC and OCSP combined.

Subgroup	Events / Patients	Risk(%)	95% CI
Definition A			
PACI	54 / 264	22.9	17.5-28.2
POCI	28 / 151	19.5	13.0-25.9
LACI	7 / 132	5.4	1.5-9.3
TACI	4 / 110	3.9	0.1-7.6
TOTAL	93 / 657	15.1	12.3-17.9
Definition B			
PACI	26 / 264	12.5	8.0-16.9
POCI	13 / 151	10.1	4.9-15.3
LACI	4 / 132	3.2	0.1-6.2
TACI	3 / 110	3.0	0.0-6.3
TOTAL	46 / 657	8.1	5.9-10.4
Definition C			
PACI	16 / 264	8.1	4.3-12.0
POCI	8 / 151	6.6	2.2-11.0
LACI	3 / 132	2.4	0-5.0
TACI	1 / 110	1.0	0-3.0
TOTAL	27 / 657	5.0	3.1-6.8







6.5. Discussion

Analysis of data from two population-based studies with well-defined inclusion criteria and detailed follow-up has demonstrated that the definition used for recurrent stroke has a major effect on the measured risk of stroke risk at 3 months. The use of these different definitions partly explains the differences in risks of recurrent stroke that have been reported after a first-ever ischaemic stroke (e.g. one year risks of 7%,[7] 10%,[10] 12%,[3,12] and 15%[15]). We believe that the 24-hour exclusion definition of recurrence (definition A) is most clinically valid. The use of data from previous epidemiological studies that have used the more restrictive definitions in health economic and other effectiveness analyses will underestimate the potential benefits of early preventive treatment.

A standard definition of recurrent stroke is also required so that different studies can be compared or meta-analysed appropriately, time trends in risk can be determined accurately, and absolute risk reductions with treatment can be properly compared across trials. Our data suggest that comparisons are likely to be highly biased unless definitions of recurrence are the same. If information on the early clinical course of patients is insufficiently detailed to use definition A reliably in certain types of large-scale epidemiological studies, for example, and more restrictive definitions are therefore necessary, it is important that researchers be aware of the potential underestimation of risk.

It is, of course, important that progression of the initial stroke, haemorrhagic transformation of infarction, systemic disturbances, or oedema and mass effect resulting in fluctuations in cerebral perfusion, are not misclassified as recurrent strokes.[24,25] For this reason, it has been argued that neurological deterioration occurring after 24 hours should only be included as a potential recurrent stroke if the neurological deficit was clearly different from the index stroke or was of a different clinical subtype,[17] or if it occurred after an unequivocal period of neurological stability for 24 hours.[14-16] These stipulations are reasonable, although it

should be noted that early recurrence is most common after minor ischaemic stroke, in which haemorrhagic transformation, oedema and mass effect, and systemic disturbances are least likely.

It is also important to note the use of the different definitions also leads to biases in analyses of the relationships between risk of recurrence and subtype of stroke. For clinical subtype, there was no significant difference in risk of recurrence when definition C was used, but there was highly significant heterogeneity with definition A, with higher risks in patients with PACI and POCI strokes. This difference is due to the fact that recurrent events tend to occur early in these subtypes of stroke. Patients with PACI have the highest prevalence of carotid stenosis, which has been shown to be associated with a high early risk of stroke, [11,14-16] and a high proportion of POCI strokes are thought to be due to large artery atherosclerosis.[26] Indeed, the risk of recurrent stroke following a posterior circulation TIA or minor stroke in published studies is significantly higher than that in patients with carotid territory events in studies with follow-up which commenced at the time of the event, but significantly lower in studies in which patients were recruited after the acute phase.[27]

Our study has a number of potential shortcomings. First, we were reliant on the accuracy of the clinical recording of recurrent events. However, we were conservative in our definition of possible recurrent stroke, only including sudden acute neurological deterioration if there was considered to be a low probability that it was due to oedema, brain swelling, seizures, drugs or other potential complications of stroke, or if there was definite evidence of recurrent stroke on brain imaging. The low early risk of recurrent stroke in patients with TACI syndromes suggests that we were not misdiagnosing non-specific neurological deterioration as stroke. If anything, we may have underestimated the early risk of recurrent events, particularly minor strokes, because patients were not reviewed between hospital discharge and one month unless they sought medical attention with a further event.

Second, we excluded sudden acute neurological deterioration that occurred within 24 hours of the onset of the initial stroke. Such early events have not previously been regarded as recurrent strokes, partly because the initial event cannot strictly be called a stroke based on current definitions before 24 hours have elapsed.[28] However, early deteriorations do occur in over 10% of patients randomised in acute stroke trials, in the absence of signs of raised intracranial pressure or haemorrhagic transformation,[29] and are often associated with new ischaemic lesions of brain imaging.[30] Sudden deterioration within 24 hours in patients who had not recovered from their initial event may therefore represent potentially preventable recurrent ischaemic episodes. Interestingly, in the NINDS rt-tPA Stroke Trial placebo arm patients not on aspirin at the time of their stroke were more likely to have early clinical deterioration.[31]

6.6. Conclusion

We have shown that the risk of recurrence after first-ever ischaemic stroke varies several-fold depending on the definition used, and that the definitions that are most widely used in epidemiological studies substantially underestimate the risk, particularly in patients with PACI and POCI syndromes. A standard definition of recurrent stroke is required so that different studies can be compared or meta-analysed appropriately, time trends in risk can be determined accurately, and absolute risk reductions with treatment can be properly compared across trials. Comparisons are likely to be highly biased unless definitions of recurrence are the same.

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Chapter 7

A population-based study of the early risk of stroke after a TIA or minor stroke: Implications for public education and organisation of services

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7.1. Abstract

Objectives: To estimate the very early stroke risk after a transient ischaemic attack (TIA) or minor stroke and thereby inform the planning of effective stroke prevention services.

Design: Population-based prospective cohort study of patients with TIA or stroke.

Setting: Nine general practices in Oxfordshire, UK, from April 2002 to April 2003.

Participants: All patients who had a TIA (n=87) or minor stroke (n=87) during the study period and who presented to medical attention.

Main outcome measures: The risk of recurrent stroke at 7 days, 1 month and 3 months of TIAs and minor strokes.

Results: The estimated recurrent stroke risks at seven days, one month and three months were 8.0% (95%CI=2.3–13.7), 11.5% (95%CI=4.8–18.2) and 17.3% (95%CI=9.3-25.3) respectively after a TIA, and 11.5% (95%CI=4.8-21.2), 15.0% (95%CI=7.5-22.5) and 18.5% (95%CI=10.3-26.7) respectively after a minor stroke.

Conclusions: The early risks of stroke after a TIA or minor stroke are much higher than commonly quoted. More research is required to determine whether these risks can be reduced by more rapid instigation of prevention treatment.

7.2. Introduction

Approximately 15% of ischaemic strokes are preceded by a transient ischaemic attack (TIA).[1] This "warning" event provides an opportunity to prevent stroke, and guidelines highlight the need for rapid-access clinics.[2-4] However, although there has been much work on the causes and dangers of delayed assessment after acute major stroke,[5,6] there have been few studies of TIA or minor stroke, and it is therefore uncertain how urgently patients must be seen for these clinics to be effective. North American guidelines suggest that assessment and investigation should be completed within one week of a TIA or minor stroke,[7,8] and UK guidelines recommend assessment within two weeks,[2,3] but there is great variation in routine practice.[9] In the UK, the National Service Framework for older people requires that rapid access stroke prevention services are in place by April 2004.[4] However, no guidance is given for how rapidly patients should be seen.

The danger of delaying investigation and treatment after a TIA or minor stroke depends on the early risk of subsequent stroke. Commonly quoted risks, of 1-2% at seven days, and 4% at one month,[1,10-14] are underestimates because patients were usually recruited several weeks after the TIA. Any patients who had a major stroke during this period were excluded. An emergency department study of patients presenting within 24 hours of TIA, reported a stroke risk of 5.3% at two days,[15] but there are no recent data from population-based studies, and there are no data on the risk of recurrence after minor stroke, which is also usually investigated in "TIA" clinics.

We have studied the early risk of stroke after a TIA or minor stroke in a prospective population based study (Oxford Vascular Study, OXVASC), in which patients are enrolled as soon as possible after their symptoms and detailed information is collected on the timing of symptom onset and early recurrent events.

7.3. Methods

The OXVASC study is a population-based study of the incidence and prognosis of TIA and stroke.[16] The methods and population are similar to those in the Oxfordshire Community Stroke Project (OCSP; 1981-1986).[17] The study covers a population of 90,542, registered with 63 general practitioners (GPs), in 9 family health centres in Oxfordshire, UK. Registration of patients into the first year began on 1st April 2002 and continued until 31st March 2003, and was approved by the Oxfordshire Clinical Research Ethics Committee (Ref: C0.043).

Collaborating GPs were encouraged to immediately notify the study physician by telephone, pager or facsimile of any patient whom they thought might have had a TIA or stroke. Regular checks were made to ensure that all relevant patients were referred, by means of a liason GP in each practice, a bimonthly visit to each practice from the study research nurse, frequent personal contact between the study physicians and the GPs, and practice diagnostic code searches. Patients presenting to hospital were ascertained by daily review of hospital admission registers, emergency department attendance records, the John Radcliffe Hospital stroke unit, medical admissions and other relevant wards, and by regularly checking all brain and carotid imaging requests. Patients not requiring hospital admission were seen as soon as possible by a study physician in a daily (Monday to Friday) clinic, or assessed in the community. The date and time of onset of each vascular event, and the date and time that each patient first sought medical attention, were recorded. In addition to standard ascertainment, follow-up was performed by face-to-face interview with a study nurse at one and three months. If a recurrent event was suspected the patient was re-examined by a study neurologist (PMR).

Patients were included in this analysis if they presented with a first or recurrent TIA or minor stroke during the study period, diagnosed according to standard criteria.[18,19] Minor stroke was defined as ≤3 on the NIH stroke scale[20] at time of initial assessment. Patients were excluded if they did not give informed consent or if

assent from the nearest relative was unavailable. Actuarial survival free of stroke was calculated from the time of onset of the first TIA or the first minor stroke during the study period.

7.4. Results

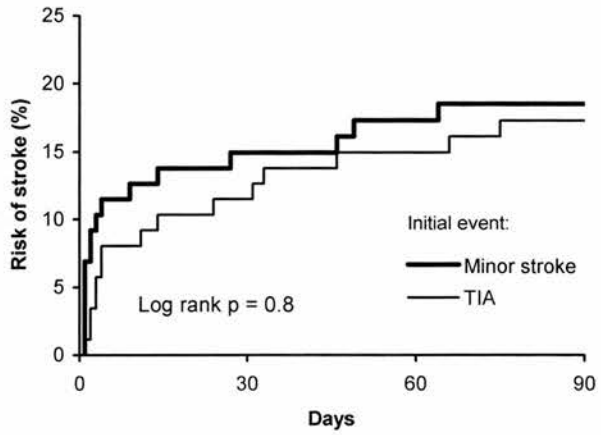
We recruited 87 patients with a TIA, and 87 patients with a minor stroke (table 7.1). 83 OXVASC patients with major stroke (NIH score >3) were excluded. All patients were followed up for 3 months. During this time 15 TIA patients had a subsequent stroke, two of which were fatal and three of which resulted in an increased Rankin score[21] at three months follow-up. The remaining ten were minor strokes and were therefore entered into the minor stroke analysis from the date of the minor stroke onwards. Sixteen minor stroke patients had a subsequent stroke, of which four were fatal and two resulted in increased disability at three months. For TIA patients, the estimated stroke risks were 8.0% (95%CI=2.3–13.7) at seven days, 11.5% (95%CI=4.8–18.2) at one month, and 17.3% (95%CI=9.3-25.3) at three months. These risks were similar (log rank p=0.8, figure 7.1) in minor stroke patients: 11.5% (95%CI=4.8-21.2), 15.0% (95%CI=7.5-22.5) and 18.5% (95%CI=10.3-26.7), respectively.

Five TIA patients and three minor stroke patients had their subsequent stroke before seeking medical attention after the initial event. If these patients are excluded to produce more conservative estimates, the seven-day, one-month and three-month stroke risks are 7.2% (95%CI=1.7–12.8), 8.4% (95%CI=2.4–14.4), and 13.3% (95%CI=6.0–20.6), respectively, after a TIA, and 7.2% (95%CI=1.7–12.8), 10.9% (95%CI=4.2–17.6), and 14.6% (95%CI=7.0–22.2), respectively, after a minor stroke.

Table 7.1. Characteristics of patients included in the analyses

Characteristics	TIA patients	Minor stroke patients
Mean age (SD)	75.0 (10.8)	73.0 (12.5)
Male Sex	38 (44%)	41 (47%)
Previous TIA or stroke	36 (41%)	19 (22%)
Treated hypertension	48 (55%)	47 (54%)
Current smoking	5 (6%)	19 (22%)
Treated Diabetes Mellitus	10 (12%)	10 (12%)
Angina	18 (21%)	16 (18%)
Previous MI	16 (18%)	16 (18%)
History of treated hyperlipidaemia	28 (32%)	21 (24%)
Antiplatelet therapy before event	44 (51%)	36 (42%)
Anticoagulated before event	6 (7%)	1 (1%)
Total:	**87**	**87**

Figure 7.1. Cumulative risk of stroke following TIA or minor stroke



7.5. Discussion

Our results support the findings of a recent re-analysis of the OCSP data which showed similarly high risks of stroke after a first ever TIA.[22] However, the OCSP analysis was based on data collected 20 years ago, when fewer patients were likely to be taking stroke prevention treatments, and did not include patients with minor stroke. Our more recent data have important clinical implications. If patients present to medical attention very soon after TIA or minor stroke, either in general practice or in the emergency department, the risk of stroke is high and urgent preventive treatment is required. This is particularly important for patients in whom specific treatments are indicated, such as those with cardiac embolism or carotid stenosis. Patients with atrial fibrillation require anticoagulation,[23] and benefit from carotid endarterectomy falls rapidly with time after a TIA or non-disabling stroke.[24] UK guidelines recommend that TIA and minor stroke patients should be seen in clinics within two weeks,[2,3] but our data show that a substantial number of patients will have a stroke prior to being seen in such clinics. For stroke prevention to be most effective, patients will need to be seen within the first few hours or days.

Delays before patients are included into studies lead to underestimation of the risk because strokes occurring during this time are excluded. We minimised these delays in our study by prompt evaluation of patients in a daily clinic. Nevertheless, a short delay is unavoidable, and a few patients in our study who had a recurrent stroke before seeking medical attention for the initial TIA or minor stroke were therefore included retrospectively. This can result in an overestimation of the risk, because an unknown number of patients who had no recurrent event and who never presented to the study are excluded. However, only eight patients were ascertained retrospectively, and exclusion of these cases did not significantly alter our results.

7.6. Conclusion

The estimated risk of stroke after a TIA or minor stroke is 8-12% at seven days, and 11-15% at one month. For stroke prevention to be effective, the public would need to be educated to seek medical attention urgently, and services organised such that all patients with TIA or minor stroke are seen immediately. Further research is required to determine the most effective strategy to prevent early recurrent stroke.

7.7. References

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Chapter 8

Early risk of recurrence by subtype of ischaemic stroke in population-based incidence studies

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8.1. Abstract

Background

Data on the early risk of recurrent stroke by aetiological subtype are important for the organization of stroke prevention.

Objective

To study the early risk of recurrent stroke by aetiological subtype.

Methods

We studied risk of recurrent stroke by aetiological subtype (TOAST classification) in patients in two population-based studies: the Oxford Vascular Study and the Oxfordshire Community Stroke Project. We performed a meta-analysis with data from the only two other published studies reporting equivalent data.

Results

The four studies included 1709 strokes with 30 recurrences at 7 days, 72 at 30 days and 113 at 3 months. Recurrent stroke risk varied between subtypes ($p<0.001$). Compared with other subtypes, patients with stroke due to large artery atherosclerosis (LAA) had the highest odds of recurrence at 7 days (OR=3.3, 95%CI=1.5-7.0), 30 days (OR=2.9, 95%CI=1.7-4.9) and 3 months (OR=2.9, 95%CI=1.9-4.5). Odds of recurrence at 30 days for other subtypes were: cardioembolic (OR=1.0,

95%CI=0.6-1.7); undetermined (OR=1.0, 95%CI=0.6-1.6); and small vessel stroke (OR=0.2, 95%CI=0.1-0.6). There was no significant heterogeneity between the studies. Although only 14% of strokes were associated with LAA, this subtype accounted for 37% of recurrences within 7 days.

Conclusions

The risk of early recurrent stroke is highest in patients with large artery atherosclerosis. This supports the need for urgent carotid imaging and prompt endarterectomy.

8.2. Introduction

The risk of recurrent stroke is highest in the first few weeks after a first TIA or stroke.[1-3] Guidelines suggest that assessment and investigation of TIA or minor stroke should be completed quickly: 1 week in North America,[4] and 2 weeks in the UK.[5] However, there is variation in routine practice.[6] It is important to obtain more information about which patients are at highest early risk of stroke and which investigations are therefore most urgent. The risk of early recurrent stroke is likely to be related to the underlying pathology. For example, the risk of stroke in patients with symptomatic severe carotid stenosis can be as high as 5% per week during the period prior to endarterectomy.[7] However, in previous population-based studies on the early risk of recurrent stroke by aetiological subtypes,[8,9] the numbers are too small to reliably compare subtypes or to determine the risk of recurrence within seven days. Therefore, we compared the early risk of stroke in different aetiological subtypes of ischaemic stroke using all available data from high-quality population based studies. We report new data from two UK studies and have combined these in a meta-analysis with data from two other studies found in a systematic review of the literature.

8.3. Methods

Oxford Vascular Study (OXVASC) and Oxfordshire Community Stroke Project (OCSP)

We studied the early risk of recurrent stroke according to subtype of ischaemic stroke in two UK population-based studies: the OCSP (1981-1986) and the first year of the OXVASC study (2002-2003). The methods and results of the OCSP have been previously published.[3,10] The OXVASC pilot study used identical methods of ascertainment of stroke and TIA to the OCSP (see chapter 2).[10,11] Briefly, by collaboration with Family Physicians (FPs) (63 in OXVASC, 50 in the OCSP), an urban and rural population (91,000 in OXVASC, 105,000 in OCSP) was studied. FPs were encouraged to report all patients who might have suffered a TIA or stroke during the study periods. Strokes were also identified by daily assessment of hospital registers, hospital diagnostic coding, review of referrals for brain and vascular imaging, regular visits to all general practices, and review of all death certificates and coroner's reports where relevant. In both studies, a study physician assessed all cases as soon as possible after notification. Details of the presenting event, clinical characteristics, and medical history were recorded from the patient, FP records and hospital records. Study methods conformed to the quality criteria for population-based stroke incidence studies.[12]

Investigation and stroke prevention treatments

In OXVASC, all patients had neuroimaging (normally CT), ECG, and carotid ultrasound, when possible and usually on the day of the clinical assessment. In the OCSP, patients also routinely had CT brain imaging and ECG. However, Doppler ultrasound was not available, and patients underwent intra-arterial carotid angiography if there was a clinical suspicion of large vessel disease. In both studies, echocardiography and 24 hour ECG monitoring was performed when there was a clinical suspicion of cardiac pathology.

In OXVASC, patients received an antiplatelet agent (at least acetylsalicylic acid, ASA), a statin and blood pressure lowering therapy where there are no contraindications to treatment. In the OCSP, most patients received antiplatelet therapy (eligible patients were randomised in the UK-TIA trial,[13] and had a two in three chance of receiving ASA), and hypertensive patients received blood pressure lowering therapy. OXVASC patients with symptomatic severe carotid stenosis (> 70%) were referred for endarterectomy. The equivalent subgroup of patients in the OCSP were randomized in the European Carotid Surgery Trial (ECST).[14]

Classification of stroke subtype

In OXVASC, patients routinely had Doppler scanning of the carotid and vertebral arteries and echocardiography. Stroke aetiology was classified prospectively according to the TOAST criteria, on completion of the investigations.[15] In 50 consecutive OXVASC cases of ischaemic stroke, two observers independently classified the aetiology according to the TOAST criteria to determine inter-observer reproducibility. In the OCSP, the subtype of ischaemic stroke had been classified according to the OCSP classification,[16] but the investigators had also originally prospectively categorized stroke according to aetiology. Detailed clinical and imaging data were also collected. This allowed us to re-classify all ischaemic strokes according to the same aetiological categories as used in the TOAST study, using a simple algorithm.[15,17] It has been shown that this method of TOAST classification can be applied retrospectively and that this is accurate and reproducible.[17] We were able to adhere to the exact TOAST criteria for all the aetiological categories with the exception of large vessel strokes because Doppler ultrasound was not routinely available at the time of the OCSP. Carotid disease (> 50% stenosis of an appropriate vessel) was diagnosed by arterial angiography, which was only performed if large vessel disease was suspected because of the clinical assessment. Therefore, the LAA definition in the OCSP was based primarily on the angiographic imaging. However, we also included some strokes where the original investigators had a high index of clinical suspicion of LAA, but angiography could not be performed.

Recurrent strokes

Patients in OXVASC were followed up at one, three, six, nine and twelve months, and annually thereafter. OCSP patients were followed up at one, six and twelve months and then annually. Recurrent vascular events were also identified at the time of the event as part of the ongoing case ascertainment in the incidence study. Recurrent stroke was defined as a new neurological deficit fitting the standard definition of a stroke,[10] which occurred after a period neurological stability or improvement lasting at least 24 hours. This definition excluded any new deficit which occurred within 24 hours, or which was thought to be attributable to edema, mass effect or hemorrhagic transformation of the incident infarct. All recurrences within 3 months were reviewed independently by two study neurologists.

Systematic review

To identify population-based stroke incidence studies that reported data on the early risk of recurrent stroke according to the TOAST classification of ischaemic stroke (or similar) we:

1. Identified all stroke incidence and prognosis studies referenced in previously published reviews, and searched Medline and Embase for any follow-up or secondary studies using the author and study names from the primary study.

2. Performed a further search of Medline using the following search terms: "stroke and incidence" and "stroke and subtype".

3. Hand-searched the journals *Stroke* and *Cerebrovascular Diseases* from 1990-2002.

We had four main inclusion criteria. Firstly, studies had to be population-based studies of stroke incidence and outcome that satisfied the 12 quality criteria published previously.[12] Secondly, studies should have ascertained strokes in all sections of the population, rather than in specific racial groups.[16] Thirdly, studies

must have had a combined brain-imaging or autopsy rate of at least 80%. Finally, studies must have reported the frequency of early recurrent stroke (within three months) for incident cases of ischaemic strokes classified according to the TOAST criteria or a comparable classification. Although the study designs had to be broadly comparable, there are still likely to be differences between studies in the reliability of identification of early recurrent strokes, and the differentiation between an early recurrence and a deterioration of the primary event. Therefore, different rates of recurrence were expected between studies and so we restricted our analyses to within study comparisons.

Statistical analyses

Patients who suffered a recurrent stroke secondary to a vascular intervention, such as endarterectomy or angiography, were excluded from the analyses. For patients in OXVASC and OCSP, the actuarial risk of recurrent stroke was determined by Kaplan-Meier analysis for each aetiological subtype for the first 90 days. Heterogeneity was tested with the log-rank test. We compared the risk of recurrent stroke between the subtypes (e.g. large artery *vs* the rest) in a Cox regression analysis, and corrected for age, sex, treated diabetes, daily smoking, and treated hypertension.

For each study in the meta-analysis, the number of recurrent strokes at seven days, one month and three months was recorded for each aetiological subtype. We compared the odds of having a recurrent stroke for each aetiological subtype with the odds of recurrence in the remainder. We also compared the odds of having a recurrent stroke between individual subtypes eg. large artery vs small vessel etc. In the meta-analysis, the odds ratios from individual studies were combined to produce pooled estimates using the Mantel-Haenzel-Peto method.

8.4. Results

OXVASC and OCSP stroke-free survival analyses

151 patients with proven ischaemic stroke in the OXVASC study (1st April 2002 – 31st March 2003) and all 577 patients with proven ischaemic stroke in the OCSP (1981-1986) were included in the survival analyses (table 8.1). Combined brain imaging and autopsy rates were 96% in OXVASC and 81% in OCSP.

Four patients (2.6%) in the OXVASC study underwent carotid endarterectomy within three months. No patients in OXVASC underwent endarterectomy within 1 month. In the OCSP, four patients were randomized to surgery in the ECST. Of these, one underwent endarterectomy within one month, and two patients underwent endarterecomy after one month but within three months of symptoms. No patients in either study suffered a recurrent stroke as a result of a vascular intervention.

There was good inter-observer agreement for the assignment of the TOAST classification in 50 consecutive patients in OXVASC (86%, kappa = 0.81, 95% CI = 0.67 – 0.94). There was no difference between the two studies in the relative proportions of the four major TOAST subtypes (p = 0.1). Therefore the data in these two studies were combined for the survival analyses.

There was heterogeneity between the four major TOAST subtypes for the three-month risk of recurrent stroke (log rank $p < 0.001$). Patients with large artery atherosclerosis (LAA) had the highest actuarial risk of recurrent stroke at three months (19.2%, 95% CI = 11.2 – 27.2% vs 8.1%, 95% CI = 5.8 – 10.4% in the rest; OR = 2.6, 95% CI = 1.5 – 4.4, p = 0.001, figure 8.1). LAA was related to a higher risk of recurrent stroke at three months compared to the rest after correction for source study, age, sex, diabetes, hypertension and smoking (OR = 2.3, 95% CI = 1.3 – 3.9, p = 0.004).

Table 8.1. Characteristics of patients included in the four studies included in the meta-analysis.

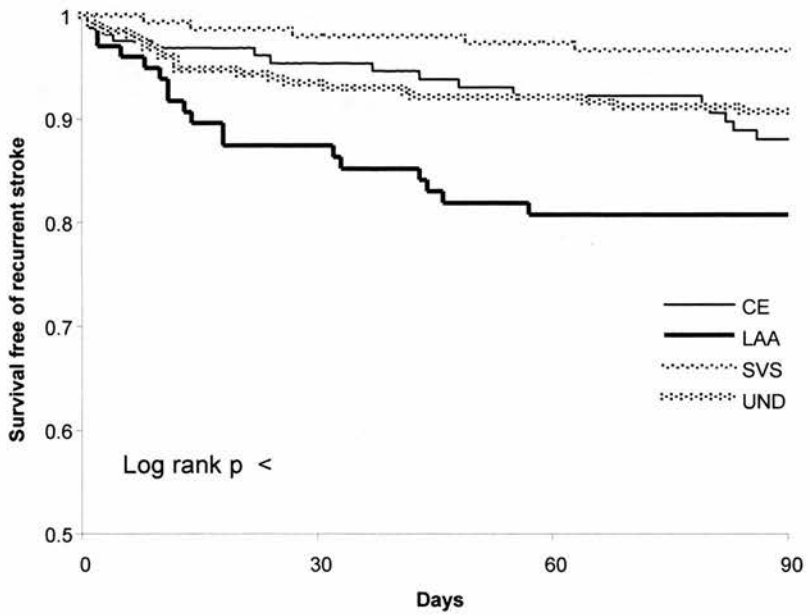
Patient characteristics	OXVASC	OCSP	Erlangen	Rochester
Mean age in years (SD)	76 (11)	73 (13)	73 (13)	76 (*)
Male sex	70 (46.4%)	281 (48.7%)	315 (41.9%)	184 (40.5%)
Hypertension**	88 (53.3%)	270 (46.8%)	305 (57.4%)	331 (72.9%)
Diabetes Mellitus***	16 (10.6%)	60 (10.4%)	130 (24.5%)	94 (20.7%)
Current Smoking	28 (18.5%)	154 (26.7%)	71 (13.4%)	221 (48.7%)
Recurrent stroke < 3 months	23 (15.2%)	40 (6.9%)	17 (3.2%)	33 (7.3%)
Aetiological subtypes:				
Large artery atherosclerosis	26 (17.2%)	78 (13.5%)	71 (13.4%)	74 (16.3%)
Small vessel stroke	33 (21.9%)	119 (20.6%)	120 (22.6%)	72 (15.9%)
Cardioembolic	37 (24.5%)	127 (22.0%)	143 (26.9%)	132 (29.1%)
Undetermined	54 (35.8%)	220 (38.1%)	188 (35.4%)	164 (36.1%)
Other	1 (0.7%)	33 (5.7%)	9 (1.7%)	12 (2.6%)
Total	151	577	531	454

* data not available

** history of hypertension or blood pressure > 160/95 prior to stroke

*** differences in the definition of diabetes mellitus existed between the studies

Figure 8.1. Three-month survival free of recurrent stroke by TOAST subtype for patients in OXVASC and the OCSP. The corresponding actuarial risks of recurrent stroke in each subtype are given below the figure with 95% confidence intervals.



	Actuarial recurrent stroke risks (95%		
	At 7 days	**At 1 month**	**At 3 months**
SVS	0%	2.0% (0–4.2)	3.4% (0.5–6.3)
CE	2.5% (0.1–4.9)	4.6% (1.3 – 7.9)	11.9% (6.4–17.4)
UND	2.3% (0.5-4.1)	6.5% (3.4-9.6)	9.3% (5.6-13.0)
LAA	4.0% (0.2-7.8)	12.6% (5.9-19.3)	19.2% (11.2 – 27.2)

Systematic review and meta-analysis

We identified 22 published population-based stroke incidence studies in which brain imaging or autopsy had been performed in 80% or more. However, only two studies reported the early risk of recurrent stroke by aetiological subtype of ischaemic stroke.[8,9] The meta-analysis therefore included these two previous studies, the OXVASC study and the OCSP. The clinical characteristics for each study by aetiological subtype have been reported previously.[18] In the Rochester and Erlangen studies, combined brain imaging and autopsy rates were 92% and 94%.

The total number of patients was 1713. The number of patients undergoing endarterectomy or other vascular intervention were not available for the Rochester or Erlangen study. However, it was reported in the Rochester study that four patients who had LAA had a recurrent stroke within the first month secondary to interventions. These patients were excluded from all analyses. There were no cases in OXVASC or OCSP and no reported cases in the Erlangen study of intervention-related stroke. Of the remaining 1709 patients, 30 (1.8%) suffered a recurrent stroke within 7 days, 72 (4.2%) within 30 days, and 113 (6.6%) within three months.

Figure 8.2 compares the risk of recurrent stroke at one month of LAA strokes with other aetiological subtypes. Patients with LAA had the greatest risk of recurrence at one month (OR = 2.9, 95% CI = 1.7 – 4.9, $p < 0.001$) and also at 7 days (OR = 3.3, 95% CI = 1.5 – 7.0, $p = 0.003$) and three months (OR = 2.9, 95% CI = 1.9 – 4.5, $p < 0.001$). The patients with small vessel stroke showed the lowest risk of recurrent stroke at one month (OR = 0.2, 95% CI = 0.1 – 0.6, $p < 0.003$), 7 days (OR = 0.2, 95% CI = 0.0 – 1.1, $p = 0.05$) and 3 months (OR = 0.2, 95% CI = 0.1 – 0.5, $p < 0.001$). The risks in patients with cardioembolic stroke and in patients with undetermined aetiology were not significantly different from the rest: 1 month OR = 1.0, 95% CI = 0.6-1.7, $p = 1.0$ and 1 month OR = 1.0, 95% CI = 0.6-1.6, $p = 1.0$, respectively. There was no significant heterogeneity between the four studies in any of the comparisons.

The one month odds ratio of recurrent stroke in the patients with LAA compared with SMVD was 8.4, 95% CI = 2.9-24.3, p<0.001. While only 14.3% of the total number of patients had LAA by TOAST criteria, this group accounted for 36.7% of recurrent strokes within 7 days (table 8.2). In contrast, small vessel stroke, present in 20.1% patients, accounted for only 3.3% 7-day recurrences.

Figure 8.2. Odds ratios for risk of recurrent stroke at 1 month for LAA vs other TOAST subtypes: a meta-analysis of population based studies.

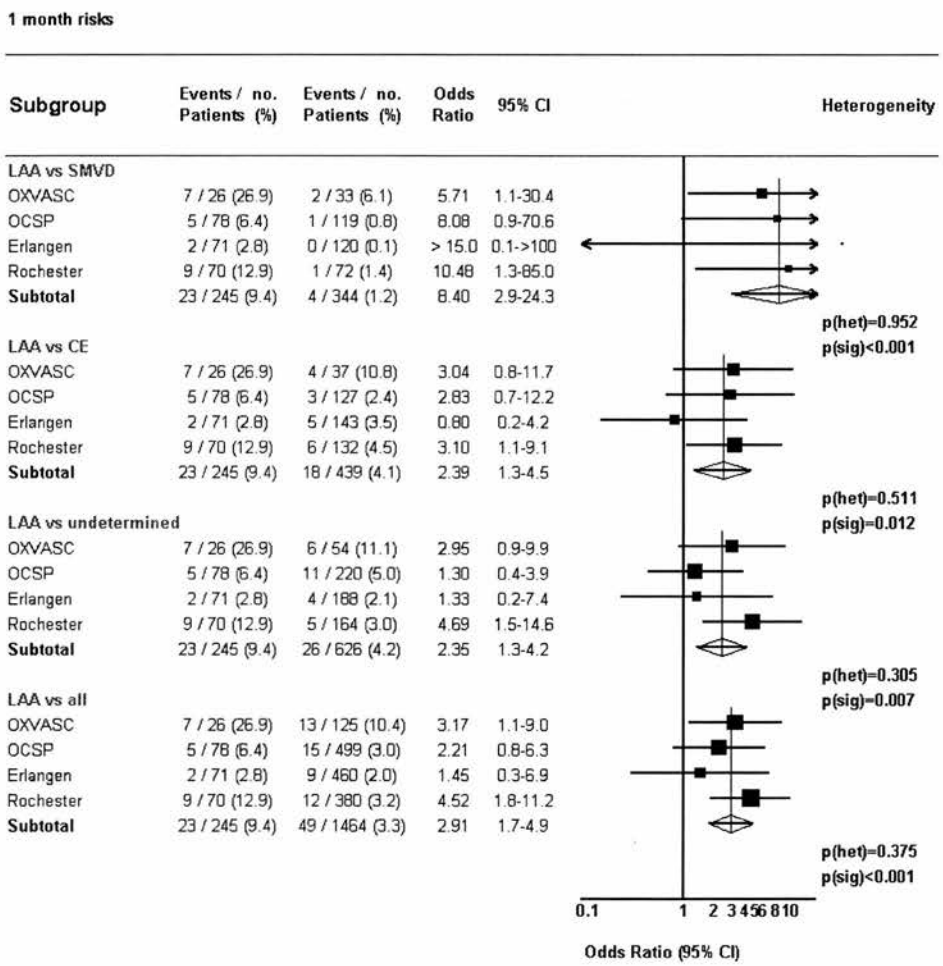


Table 8.2. Proportions of recurrences by aetiological subtype of ischaemic stroke, compared with the proportions of total patients in the four studies included in the meta-analysis.

Aetiological subtype	% total patients (n = 1709)	% 7 day recurrent strokes (n = 30, 1.8%)	% 1 month recurrent strokes (n = 72, 4.2%)	% 3 month recurrent strokes (n =113, 6.6%)
Large artery atherosclerosis	14.3%	36.7%	31.9%	31.0%
Small vessel stroke	20.1%	3.3%	5.6%	6.2%
Cardioembolic	25.7%	23.3%	25.0%	30.1%
Undetermined	36.6%	33.3%	36.1%	31.0%

Figures for strokes categorized as due to other causes are not shown because patient numbers were small.

8.5. Discussion

We found that patients with large artery cerebrovascular disease have a high early risk of recurrent stroke compared with other aetiological subgroups, whereas the patients with small vessel strokes have the lowest risk. These findings have important implications for targeting stroke prevention. Guidelines suggest that patients with TIA and stroke should be seen soon after the onset of symptoms for the implementation of stroke prevention strategies.[4,5] However, most stroke prevention treatments (e.g. cholesterol lowering agents and antiplatelet therapy) are unlikely to have an immediate effect or may be unsafe if implemented too quickly (e.g. anticoagulation, antihypertensives). In contrast, carotid endarterectomy is beneficial if implemented quickly,[19] but is only applicable to a small proportion of

patients. However, we found that only 15% of patients have LAA (mostly carotid stenosis), and one third of early recurrences occur in this group.

One potential shortcoming of the OCSP analysis was the retrospective assignment of the TOAST classification. This was unavoidable because the OCSP was conducted prior to the publication of the TOAST criteria.[10,15] However, the investigators had prospectively categorized stroke aetiology using a very similar in-house classification at the time of the study, as due to atherosclerosis, cardioembolism, small vessel disease or some other cause. We were able to use these data to classify the patients according to the TOAST criteria. The categories used were therefore the same as those defined by TOAST,[15] although imaging data were not always available for the categorization of large vessel disease. However, although fewer patients had imaging of their carotid arteries in the OCSP compared with OXVASC, the prevalence of LAA was very similar (13.5% OCSP vs 17.2% in OXVASC, table 8.1), and there was no heterogeneity between the studies for the relative risks of recurrent stroke in patients with LAA (figures 8.3). Therefore, we feel that the classification used in the OCSP was reasonable.

There are shortcomings with all aetiological classifications of ischaemic stroke. We used the TOAST classification because it is the most widely used system and because it was used in the Erlangen and Rochester studies. However, there are undoubtedly cases where aetiology, especially small vessel stroke, is not accurately identified.[20,21]

There was some variability in the overall risk of recurrence (between 1 and 4% per month) in the four studies. This may be explained by differences in the study populations or study design. For example, the differentiation of an early recurrent stroke from a deterioration resulting from the primary event, but any differences between these studies are unlikely to affect the comparisons between aetiological

subtypes of stroke within studies. The within study comparisons all showed consistent results and there was no significant heterogeneity.

Even in our meta-analysis, the total number of recurrent strokes was still relatively small because we have limited it to population-based studies. However, it is important to estimate the early risk of recurrence in an unselected group of patients. Hospitalized patients differ significantly from non-hospitalized patients in terms of aetiological subtypes, risk factors and prognosis.[18] Consequently, any estimation of risk of recurrent stroke by subtype in hospital-based studies is likely to be significantly biased because patients with milder symptoms who are not hospitalized are not usually included, and it is in this group of patients that stroke prevention is most crucial. Nevertheless, there are some data on early recurrent stroke risk by aetiological subtype in hospitalized patients, which also suggest that LAA is associated with the highest risk of recurrence in this population.[22,23]

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Chapter 9

Major reduction in stroke incidence and related risk factors in Oxfordshire, United Kingdom

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9.1. Abstract

Background

The incidence of stroke is predicted to rise because of the rapidly ageing population. However, over the past two decades, findings of randomised trials have identified several interventions that are effective in prevention of stroke. Reliable data on time-trends in stroke incidence, major risk factors, and use of preventive treatments in an ageing population are required to ascertain whether implementation of preventive strategies can offset the predicted rise in stroke incidence. We aimed to obtain these data.

Methods

We ascertained changes in incidence of transient ischaemic attack and stroke, risk factors, and premorbid use of preventive treatments from 1981–84 (Oxford Community Stroke Project; OCSP) to 2002–04 (Oxford Vascular Study; OXVASC).

Results

Of 476 patients with transient ischaemic attacks or strokes in OXVASC, 262 strokes and 93 transient ischaemic attacks were incident events. Despite more complete case ascertainment than in OCSP, age-adjusted and sex-adjusted incidence of first-ever stroke fell by 29% (relative incidence 0·71, 95% CI 0·61–0·83, p=0·0002). Incidence declined by more than 50% for primary intracerebral haemorrhage (0·47, 0·27–0·83, p=0·01) but was unchanged for subarachnoid haemorrhage (0·83, 0·44–1·57, p=0·57).

Thus, although 28% more incident strokes (366 vs 286) were expected in OXVASC due to demographic change alone (33% increase in those aged 75 or older), the observed number fell (262 vs 286). Major reductions were recorded in mortality rates for incident stroke (0·63, 0·44–0·90, p=0·02) and in incidence of disabling or fatal stroke (0·60, 0·50–0·73, p<0·0001), but no change was seen in case-fatality due to incident stroke (17·2% vs 17·8%; age and sex adjusted relative risk 0·85, 95% CI 0·57–1·28, p=0·45). Comparison of premorbid risk factors revealed substantial reductions in the proportion of smokers, mean total cholesterol, and mean systolic and diastolic blood pressures and major increases in premorbid treatment with antiplatelet, lipid-lowering, and blood pressure lowering drugs (all p<0·0001).

Conclusions

The age-specific incidence of major stroke in Oxfordshire has fallen by 40% over the past 20 years in association with increased use of preventive treatments and major reductions in premorbid risk factors.

9.2. Introduction

Stroke is the second leading cause of death worldwide[1] and the main cause of long-term neurological disability in adults, with more than half of survivors being left dependent on others for everyday activities.[2] It is also a major cause of depression, dementia, epilepsy, and falls, and patients with stroke account for more hospital and care-home bed days than any other disorder.[2] The burden of stroke is predicted to increase over the years ahead because of the rapid rise in the elderly population in both the developed and developing world. However, over the past two decades, findings of randomised trials have shown that several interventions are effective in both the primary and secondary prevention of stroke,[3-6] and researchers have estimated that full implementation of currently available preventive strategies could reduce stroke incidence by as much as 50–80%.[7,8] Country-specific data on time-trends in stroke incidence are required to assess whether implementation of these preventive strategies has been associated with any such change.

Stroke mortality rates fell from the 1950s to 1980s in North America and western Europe,[9,10] but this decline has since levelled off.[11–13] Although apparent trends in stroke mortality are very difficult to interpret because of changes over time in death certification practices and case-fatality, stroke incidence also seemed to diminish in the 1960s and 1970s in the USA,[14,15] Asia,[16] and Europe.[17–19] However, findings of most subsequent studies during the 1980s and 1990s, when effective preventive treatments had become more widely available, have shown either no change[20–24] or an increase in age-adjusted and sex-adjusted incidence.[25–31] Thus, as yet, no evidence is available that preventive strategies have reduced the incidence of stroke on a community level.

A population-based incidence study of stroke and transient ischaemic attack (the Oxfordshire Community Stroke Project; OCSP)[32,33] was undertaken in Oxfordshire, UK, 20 years ago. Because little change has taken place in either the racial mix of the population or in the organisation of the health-care system in the interim we had the opportunity to ascertain reliably the change in the incidence of stroke and transient ischaemic attack over the past 20 years. In collaboration with the original OCSP investigators, and using the same methods, we aimed to remeasure the incidence of stroke and transient ischaemic attack in the same population in 2002–04 (Oxford Vascular Study) and to compare premorbid use of preventive treatments and risk factors.

9.3. Methods

Study population

The OXVASC study population comprised all individuals, irrespective of age, registered with 63 family doctors in nine general practices in Oxfordshire, UK. In the UK, most people register with a general practice, which provides their primary health care and holds a lifelong record of all consultations with the family doctor and secondary-care providers and details of medications, blood pressure, and

investigations. OXVASC included all practices that had participated in OCSP apart from two (Thame and Deddington were excluded because they no longer refer all patients to Oxford hospitals). The remaining practices covered the same geographic areas as in OCSP, had the same referral patterns, held accurate age-sex registers of their patients, and were willing to refer any patient with a suspected cerebrovascular event to the study and allow regular searches of their computerised diagnostic coding systems. The OXVASC population was 94% white.[34] Census data suggest that this proportion has not changed since OCSP. To estimate social deprivation in the population served by our practices we used the index of multiple deprivation (IMD).[35] The electoral wards containing our practices were significantly less deprived than the rest of England (mean IMD score 8·69 vs 16·98, $p<0·0001$) but had a broad range of deprivation, with two of nine wards ranking in the lower third nationally. OXVASC was approved by our local research ethics committee.

Procedures

Diagnosis was designed to be as similar as possible to the OCSP. We used the same definitions of stroke and transient ischaemic attack.[36] Furthermore, since clinical opinion about which clinical syndromes represent transient ischaemic attack or stroke has evolved over the past 20 years, summaries of all potential cases were reviewed by the principal investigator of OCSP (CPW) to ensure that the application of definitions of events was comparable. Diagnosis was based on clinical findings and CT brain imaging as in OCSP. Furthermore, all CT scans were reviewed by a study neuroradiologist (PA) who was also involved in OCSP, and the same criteria were used for haemorrhagic infarction and primary intracerebral haemorrhage in both studies.

All events were categorised as first-ever incident or recurrent on the basis of clinical history rather than findings on brain imaging. As in OCSP, a first-ever stroke that happened in a patient with a previous transient ischaemic attack was coded as incident, but a first-ever transient ischaemic attack in a patient with a previous

stroke was coded as recurrent.[33] The other OCSP requirements for definition of an incident transient ischaemic attack were also adhered to.[33] As in the OCSP, patients who had an event while temporarily away from Oxford were included, but visitors to Oxford who were not registered with one of the study family doctors were excluded.

After a 3-month pilot study to develop rapid and effective case-ascertainment, formal ascertainment began on April 1, 2002. This report concerns strokes and transient ischaemic attacks happening up until March 31, 2004. We used the five sources of ascertainment that were used in OCSP.

(1) Collaborating family doctors reported cases to the study doctors by telephone, facsimile, or pager as soon as they became aware of a possible transient ischaemic attack or stroke. Patients not requiring immediate hospital admission were seen in a dedicated daily hospital clinic or at home if transfer to hospital was believed to be clinically inappropriate.
(2) The study team maintained frequent personal contact with the general practices by regular visits, a quarterly newsletter, and via a liaison family doctor in every practice.
(3) Computerised hospital diagnostic codes were reviewed regularly. In OCSP, the Oxford record linkage system37 was used. In OXVASC, the coding department for the Oxford Radcliffe Hospitals Trust provided a monthly general practice-specific list of all patients with ICD10 (International Classification of Diseases, 10th revision) codes for transient ischaemic attack and stroke and all deaths in hospital. A similar list was obtained from the Oxford Eye Hospital and local community hospitals.
(4) Hospital admission and emergency department registers were reviewed daily.
(5) Deaths out of hospital were identified via the Coroner's Office, by review of all death certificates in the study practices, and by ICD10 vascular death codes from the local Department of Public Health.

Three methods of case-ascertainment that were not used in OCSP were used in OXVASC.

(1) Daily visits to the acute medical admissions unit, acute stroke unit, neurology wards, and stroke rehabilitation wards, and daily contact with hospital bereavement officers to identify all patients brought into hospital dead or who died soon after arrival.
(2) A computer-generated list of all requests for brain and cerebral vascular imaging was reviewed on a monthly basis and all referrals for carotid Doppler ultrasound were reviewed every week.
(3) Patients with visual symptoms due to retinal or cerebral ischaemia were referred directly to the study from the eye emergency unit and department of ophthalmology, and lead clinical staff in the other departments (eg, paediatrics, obstetrics, etc) were contacted monthly to ascertain strokes in patients under their care.

We used two additional methods that were not used in OCSP to test the completeness of ascertainment by the methods listed above. First, all study general practice computer systems were searched every month for all patients coded with a cerebrovascular diagnosis. Second, we assessed a high-risk subset of our study population by ascertaining on a daily basis all patients admitted to hospital with an acute coronary syndrome or an acute peripheral vascular event (ruptured aortic aneurysm, acute limb or bowel ischaemia, etc) and all patients undergoing elective or emergency coronary, carotid, or peripheral vascular investigations or interventions (eg, angiography, angioplasty, endarterectomy, arterial bypass, etc). In these patients a detailed history was taken at baseline and at 1, 3, 6, and 12 months' follow-up to identify any transient ischaemic attacks or strokes happening during the study period.

A study clinician assessed patients as soon as possible after the event in hospital, in a daily dedicated clinic, or at home. Informed consent was sought, where possible, or assent was obtained from a relative. A standard clinical history and examination was done. As in OCSP, premorbid handicap and disability was assessed with the Rankin score.[38] If a patient died before assessment, we obtained an eyewitness account of the clinical event and reviewed any relevant records. We aimed to obtain CT brain imaging in every case. If death occurred outside hospital or before brain imaging, the autopsy result was reviewed. In view of the high rate (98%) of imaging and autopsy in OXVASC, strokes of unknown type were coded as ischaemic for this analysis. In OCSP, strokes that did not have brain imaging or autopsy (12%) were classified as haemorrhages only if clinical scoring systems indicated a high degree of certainty.[32] Otherwise they were coded as ischaemic for this analysis. Diagnosis of subarachnoid haemorrhage[32] and clinical subtyping of stroke[39] were the same as in OCSP.

Both OCSP and OXVASC recorded premorbid medication and vascular risk factors from the patient or relative, hospital records, and general practice records. The most recent measurement of blood pressure was recorded in both studies from the general practice records. Total cholesterol concentration was measured at the time of assessment after the transient ischaemic attack or stroke. All surviving cases were followed up by a research nurse or therapist at 1, 3, 6, and 12 months from the time of the stroke and the Rankin score was calculated. If a recurrent vascular event was suspected the patient was assessed by a study doctor.

Statistical analysis

OCSP ascertained strokes and transient ischaemic attacks initially from Nov 1, 1981, to Oct 31, 1984, and OXVASC from April 1, 2002, to March 31, 2004. The midpoints of these dates are exactly 20 years apart (April 1, 1983, and April 1, 2003) and these periods form our primary comparison. OCSP subsequently ascertained strokes again in 198632 and continued to record transient ischaemic attacks during 1985 and

1986.[33] Data from these periods were analysed separately. The original individual patient data and the 1981–84 and 1986 age-sex study population data from OCSP were used to recalculate the original incidences for the nine general practices in OXVASC. Confidence intervals for incidence were calculated assuming a Poisson distribution for the number of events. Poisson regression models, adjusted for the age and sex structures of the two populations, were used to calculate relative incidence for OXVASC versus OCSP. In neither OCSP nor OXVASC was there evidence of significant variation in incidence between general practices. Incidence of strokes of differing severity were calculated based on the Rankin score at 1 month and also in relation to the incidence of total anterior circulation strokes.[39] All incidences were standardised to the 2001 population of England and Wales. Changes between OCSP and OXVASC in premorbid risk factors and medication were ascertained and significance adjusted for differences in age and sex with regression models.

9.4. Results

476 individuals had at least one transient ischaemic attack or stroke during the study period. Of these, 262 were first-ever incident strokes (223 ischaemic strokes, 17 primary intracerebral haemorrhages, 16 subarachnoid haemorrhages, and six unknown) and 76 were recurrent strokes. 138 people presented to medical attention with at least one OCSP-compatible transient ischaemic attack during the study. Of these, 20 had a previous transient ischaemic attack, 17 had a previous stroke, and eight had both, leaving 93 individuals with an incident transient ischaemic attack. A further eight patients were ascertained retrospectively after presenting with a stroke but had not sought medical attention after their transient ischaemic attack. Such cases were not classified as incident events in the OCSP and were therefore excluded from this analysis. Nine of 355 incident events (2·5%, 95% CI 1·2–4·8) happened in non-whites, which was not significantly different (p=0·18) to the proportion in OCSP (nine of 728; 1·2%, 0·6–2·4)

Table 9.1 compares the age and sex structure of the midstudy populations. In OXVASC, the proportion of individuals aged 75 years or older was increased by 33% and those aged 85 years or older by 41%. If the age specific incidence of stroke had remained the same as in OCSP, the total number of incident strokes expected in OXVASC would be 28% greater than in OCSP (366 vs 286). In fact, the observed number of incident strokes in OXVASC was less than in OCSP (262 vs 286).

Table 9.1 Age and sex structure of the study populations and crude incidence per 1000 population of first-ever stroke

	Men		Women		Total	
	Number/number at risk	Rate (95% CI)	Number/number at risk	Rate (95% CI)	Number/number at risk	Rate (95% CI)
OXVASC (age, years)						
<35	0/22910	..	0/20063	..	0/42973	..
35–44	4/7401	0·27 (0·07–0·69)	2/6360	0·16 (0·02–0·57)	6/13761	0·22 (0·08–0·47)
45–54	9/6168	0·73 (0·33–1·38)	6/5577	0·54 (0·20–1·17)	15/11745	0·64 (0·36–1·05)
55–64	17/4798	1·77 (1·03–2·84)	16/4574	1·75 (1·00–2·84)	33/9372	1·76 (1·21–2·47)
65–74	44/3403	6·46 (4·70–8·68)	28/3435	4·08 (2·71–5·89)	72/6838	5·26 (4·12–6·63)
75–84	35/1857	9·42 (6·56–13·10)	54/2570	10·51 (7·89–13·71)	89/4427	10·05 (8·07–12·37)
≥85	17/431	19·72 (11·49–31·58)	30/995	15·08 (10·17–21·52)	47/1426	16·47 (12·10–21·91)
Total	126/46968	1·34 (1·12–1·60)	136/43574	1·56 (1·31–1·85)	262/90542	1·45 (1·28–1·63)
OCSP (age, years)						
<35	2/25034	0·03 (0·00–0·19)	4/22587	0·06 (0·00–0·25)	6/47621	0·04 (0·01–0·15)
35–44	7/5959	0·39 (0·16–0·81)	3/5777	0·17 (0·04–0·51)	10/11706	0·28 (0·14–0·52)
45–54	10/4577	0·73 (0·35–1·34)	3/4467	0·22 (0·05–0·65)	13/9044	0·48 (0·26–0·82)
55–64	44/3986	3·68 (2·67–4·94)	22/4058	1·81 (1·13–2·74)	66/8044	2·73 (2·12–3·48)
65–74	68/2766	8·19 (6·36–10·39)	56/3108	6·01 (4·54–7·80)	124/5874	7·04 (5·85–8·39)
75–84	65/1223	17·72 (13·67–22·58)	92/2006	15·29 (12·32–18·75)	157/3229	16·21 (13·77–18·95)
≥85	14/234	19·94 (10·90–33·46)	39/735	17·69 (12·58–24·18)	53/969	18·23 (13·66–23·85)
Total	210/43749	1·60 (1·39–1·83)	219/42738	1·71 (1·49–1·95)	429/86487	1·65 (1·50–1·82)

Population denominators refer to the whole study population without exclusions.

24 patients with incident stroke died before assessment by a study doctor and one had his event while abroad; he was fully investigated but refused assessment other than allowing access to his medical records. 239 (91%) of 262 patients with incident stroke were ascertained either in our daily clinic or during their admission to hospital. 147 (56%) were inpatients. A study doctor assessed all but two of the patients with incident transient ischaemic attack. The median (IQR) number of days from onset to assessment was 3 (1–9) for incident strokes and 5 (3–12) for incident transient ischaemic attacks compared with 4 (1–12) and 5 (3–11), respectively, in OCSP. The median (IQR) number of days from onset to brain imaging was 6 (2–13) in OXVASC and 8 (3–14) in OCSP.

Of the 262 incident strokes in OXVASC, 220 were ascertained by OCSP methods alone. However, the two methods of direct assessment of ascertainment suggested that this process in OXVASC was near complete. Only four incident strokes that had not been identified by our primary methods were identified by monthly searches of the primary care electronic patient records of the whole study population. Assessment and follow-up of 1103 high-risk individuals (all those who had an acute coronary or peripheral vascular event or a related elective investigation or intervention during the study period [5·5% of our study population ⩾60 years]) identified 16 incident strokes, all of which had already been ascertained by other methods.

The crude incidence per 1000 population in OXVASC was 1·87 (95% CI 1·67–2·08) for any stroke, 1·45 (1·28–1·63) for first-ever stroke, and 0·42 (0·33–0·53) for recurrent stroke. Recurrent events were not included in OCSP. Table 9.1 shows the number of incident strokes by age and sex in OXVASC and during 1981–84 in OCSP. Table 9.2 shows the overall incidence of first-ever stroke adjusted to the 2001 census population of England and Wales. There was a 29% reduction in incidence of any first stroke between 1981–84 and 2002–04 (relative incidence 0·71, 95% CI 0·61–0·83, p=0·0002). The incidence of stroke in OCSP in 1986 was non-significantly lower than

in 1981–84, but incidence in OXVASC remained lower than in the two OCSP periods combined (0·73, 0·63–0·85, p=0·0003). The standardised rates (per 1000 population) for recurrent stroke and any stroke (recurrent or incident) in OXVASC were 0·48 (0·37–0·59) and 2·10 (1·88–2·33), respectively.

Table 9.2 Standardised overall incidence per 1000 per year (95% CI) of first stroke in OCSP and OXVASC stratified by sex, age, pathological type, and degree of disability at follow-up 30 days after stroke

	1981–84 (OCSP)	1986 (OCSP)	2002–04 (OXVASC)	Relative incidence† (95% CI)	p
Any first stroke					
Men	2·26 (1·95–2·57)	1·94 (1·45–2·42)	1·50 (1·24–1·77)	0·66 (0·53–0·82)	0·006
Women	2·28 (1·98–2·59)	2·07 (1·56–2·59)	1·74 (1·44–2·03)	0·76 (0·61–0·94)	0·04
Age ≥85 years	18·31 (13·4–23·3)	19·99 (10·8–29·2)	16·36 (11·7–21·1)	0·89 (0·60–1·32)	0·67
Age <85 years	1·95 (1·76–2·15)	1·65 (1·34–1·96)	1·33 (1·15–1·51)	0·68 (0·58–0·80)	0·0002
Overall	2·27 (2·06–2·49)	2·01 (1·65–2·36)	1·62 (1·43–1·82)	0·71 (0·61–0·83)	0·0002
Pathological type					
Ischaemic stroke	1·93 (1·73–2·13)	1·73 (1·40–2·07)	1·42 (1·24–1·61)	0·73 (0·62–0·86)	0·0009
Primary intracerebral haemorrhage	0·22 (0·15–0·28)	0·22 (0·10–0·33)	0·10 (0·05–0·15)	0·47 (0·27–0·83)	0·01
Subarachnoid haemorrhage	0·11 (0·07–0·16)	0·05 (0·00–0·11)	0·09 (0·05–0·14)	0·83 (0·44–1·57)	0·57
Rankin score at 30 days					
0–1	0·52 (0·42–0·62)	0·49 (0·32–0·65)	0·55 (0·44–0·67)	1·04 (0·79–1·39)	0·75
2–3	0·75 (0·63–0·88)	0·78 (0·57–1·00)	0·47 (0·36–0·57)	0·61 (0·46–0·81)	0·002
4–6	1·00 (0·86–1·15)	0·74 (0·51–0·97)	0·60 (0·48–0·72)	0·60 (0·50–0·72)	0·0004

Table 9.2 shows incidence in 1981–84, 1986, and 2002–04 for types of stroke. Incidence in 2002–04 was reduced from that in 1981–84 for ischaemic stroke (0·73, 95% CI 0·62–0·86, p=0·0009) and primary intracerebral haemorrhage (0·47, 0·27–0·83, p=0·01) but not for subarachnoid haemorrhage (0·83, 0·44–1·57, p=0·57). Stratification of incident strokes by severity revealed no apparent reduction in incidence of minor stroke (Rankin 0–1 at 1 month; relative incidence 1·04, 95% CI 0·79–1·39, p=0·75) but a significant decline in disabling or fatal stroke (Rankin ◎2; 0·60, 0·50–0·73, p<0·0001). Also, a 60% reduction from 1981–84 to 2002–04 was found in the adjusted incidence of total anterior circulation stroke syndromes (0·56/1000 [95% CI 0·54–0·67] vs 0·23/1000 [0·15–0·30]; relative incidence 0·40, 95% CI 0·31–0·65, p=0·0003).

Adjusted mortality rates due to incident stroke (based on survival at 1 month) also fell from 0·44/1000 (0·35–0·54) during 1981–84 to 0·28/1000 (0·20–0·37) during 2002–04 (0·63, 0·44–0·90, p=0·02). However, 30-day case-fatality remained the same: 17·2% (45/262) in 2002–04 versus 17·8% (99/557) in 1981–84 (age and sex-adjusted relative risk 0·85, 95% CI 0·57–1·28, p=0·45).

Table 9.3 Overall incidence of transient ischaemic attack in OXVASC and OCSP by sex and age

	Annual transient ischaemic attack incidence per 1000 (95% CI)		
	1981–84 (OCSP)	1985–86 (OCSP)	2002–04 (OXVASC)
Crude incidence			
Men	0·37 (0·28–0·49)	0·42 (0·30–0·58)	0·35 (0·24–0·49)
Women	0·29 (0·20–0·40)	0·32 (0·21–0·46)	0·69 (0·53–0·89)
Overall	0·33 (0·27–0·41)	0·37 (0·29–0·47)	0·51 (0·41–0·63)
Standardised incidence			
Men	0·49 (0·35–0·63)	0·59 (0·40–0·77)	0·37 (0·24–0·50)
Women	0·37 (0·25–0·49)	0·46 (0·29–0·63)	0·77 (0·57–0·96)
Overall	0·43 (0·34–0·52)	0·52 (0·40–0·65)	0·58 (0·46–0·69)
Standardised incidence by age			
≥85 years	0·66 (0·00–1·56)	3·88 (1·01–6·76)	6·41 (3·45–9·38)
<85 years	0·42 (0·33–0·52)	0·45 (0·34–0·57)	0·46 (0·35–0·56)
<75 years	0·27 (0·20–0·34)	0·33 (0·23–0·43)	0·24 (0·17–0·32)

Direct standardisation to the 2001 census population of England and Wales was used.

By contrast with the reduction in stroke incidence, adjusted incidence of transient ischaemic attack rose slightly in OXVASC (relative incidence 1·27, 95% CI 0·95–1·71, p=0·12); however, changes in men and women were significantly different (p=0·0006), with slightly reduced incidence in men (0·76, 0·49–1·19, p=0·25) but an increase in women (1·98, 1·32–2·99, p=0·003, table 9.3). However, these findings could be biased by under-ascertainment of transient ischaemic attack in OCSP. Figure 9.1 compares the age-specific incidence curves for transient ischaemic attack

in OXVASC and OCSP. The increase in incidence with age was less steep in OCSP than in OXVASC at age 65 or older and incidence seemed to fall at age 85 or older in OCSP. A slightly reduced incidence of transient ischaemic attack was noted in OXVASC compared with 1981–84 and 1985–86 in individuals younger than 75 years, and the sex difference was less pronounced (p=0·05): males, relative incidence 0·63, 95% CI 0·36–1·09; females 1·47, 0·79–2·74.

To identify any similar under-ascertainment of stroke in the elderly, we compared the incidence of minor stroke by age in 1981–84 and 2002–04 (figure 9.1). Premorbid Rankin scores in elderly people are sometimes 2 or more 1981–84 (n=429) 1986 (n=128) 2002–04 (n=262) p* and thus a crude analysis of incidence of non-disabling stroke by age (based on post-stroke Rankin score) would lead to an artifactual reduction in incidence with age. We therefore analysed the incidence of any stroke with a Rankin score of less than 2 at 1 month or any stroke in a patient with a premorbid Rankin score of 2 or more in which the post-stroke Rankin score was unchanged. A fall was recorded in incidence of minor stroke at age 85 or older in OCSP but not in OXVASC. The age-sex incidence curves were, however, similar for non-minor stroke (figure 9.1). The change in incidence of non-minor stroke (relative incidence 0·61, 95% CI 0·50–0·75, p<0·0001) is likely, therefore, to provide the best estimate of the true change in stroke incidence between 1981–84 and 2002–04.

Figure 9.1 Age-specific incidence of transient ischaemic attack, minor stroke, and non-minor stroke. Error bars are 95% CI.

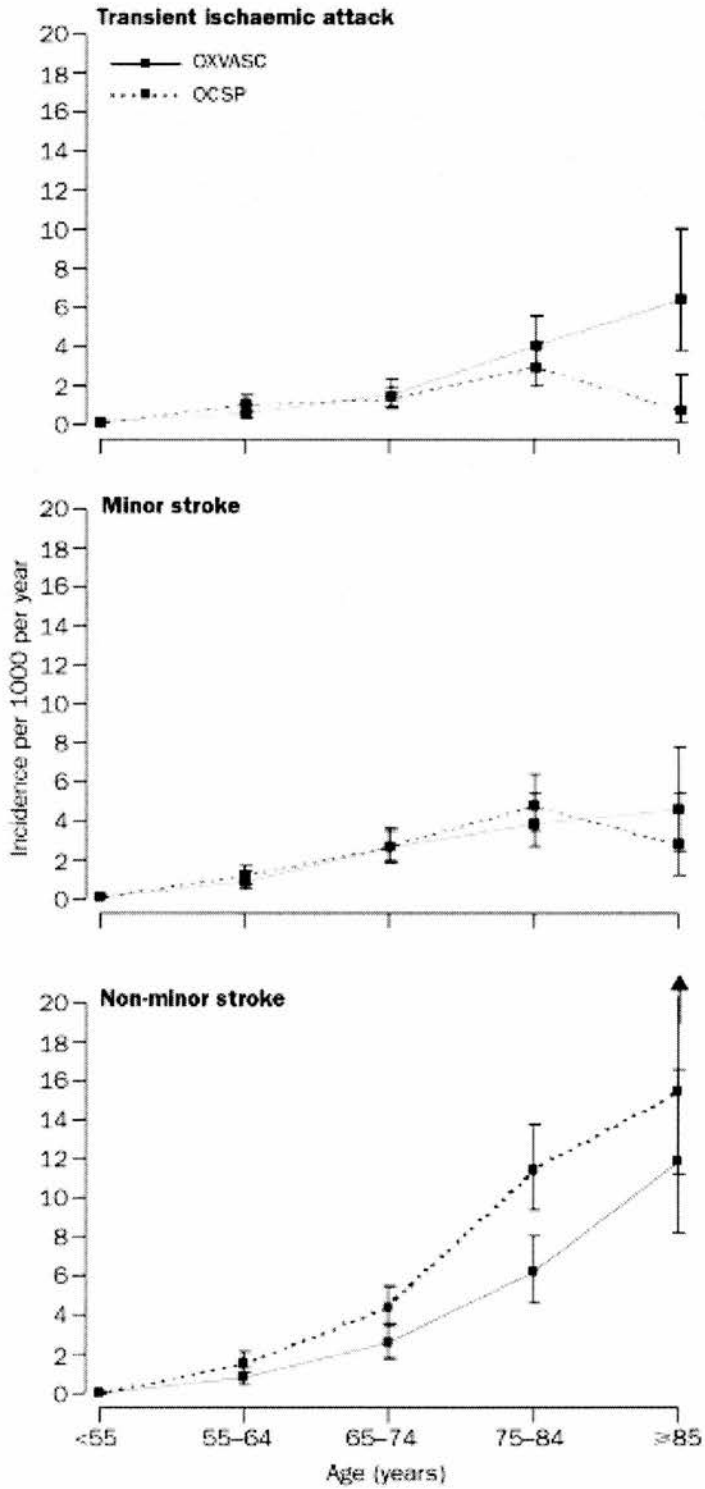


Table 9.4 shows data for premorbid risk factors and vascular preventive medication for patients with incident first-ever stroke in OCSP and OXVASC, and table 9.5 shows data for patients with incident first-ever transient ischaemic attack. Similar changes were present in both analyses. Significant reductions were recorded in mean values for the most recent premorbid measurements of systolic and diastolic blood pressure and for mean total cholesterol concentration on admission or assessment in 2002–04 compared with 1981–84. For example, in patients with transient ischaemic attack, we recorded a 12·6/7·0 mm Hg reduction in blood pressure and a 40% decrease in the proportion of patients with diastolic blood pressure 90 mm Hg or more and with systolic blood pressure 160 mm Hg or more. The median (IQR) time from most recent premorbid blood pressure measurement was 7 months (2–23) in OXVASC and 11 months (3–34) in OCSP (p=0·007). Also, a 1·3 mmol/L reduction was noted in mean total cholesterol concentration between 1981–84 and 2002–04 and a nearly 50% reduction in patients with values of 6·0 mmol/L or greater. A significant reduction in the number of patients who were regular smokers before the event was also seen. In both incident transient ischaemic attacks and strokes, the proportions of patients taking antiplatelet drugs, blood pressure lowering drugs and lipid-lowering drugs were all significantly greater. All the above changes were independent of differences in age and sex between OCSP and OXVASC cases.

Table 9.4 Premorbid risk factors and medication in patients with incident stroke

	1981–84 (n=429)	1986 (n=128)	2002–04 (n=262)	p*
Baseline characteristic				
Male sex	210 (49·0%)	62 (48·4%)	126 (48·1%)	0·83
Mean (SD) age	72·3 (12·7)	70·6 (15·3)	73·6 (11·9)	0·18
Premorbid medication				
Treated hypertension	85 (19·8%)	26 (20·3%)	124 (47·3%)	<0·0001
One drug	52 (12·1%)	19 (14·8%)	61 (23·3%)	
Two drugs	31 (7·2%)	6 (4·7%)	45 (17·2%)	
Three drugs	2 (0·5%)	1 (0·8%)	18 (6·9%)	
Antiplatelet agent	16 (2·9%)	6 (4·7%)	88 (33·6%)	<0·0001
Anticoagulant	5 (1·1%)	0 (0%)	10 (3·8%)	0·02
Lipid-lowering drug	0 (0%)	0 (0%)	29 (11·1%)	<0·0001
Premorbid risk factor				
Total cholesterol (mmol/L)				
Mean (95% CI) baseline concentration	6·24 (6·10–6·39)†	6·21 (5·95–6·47)‡	5·40 (5·26–5·54)§	<0·0001
Proportion ≥6·0 mmol/L	203 (57·5%)	64 (58·7%)	70 (29·5%)	<0·0001
Systolic blood pressure (mm Hg)				
Mean (95% CI) most recent measurement	156·3 (153·6–159·0)¶	152·9 (147·9–157·9)‖	147·6 (144·8–150·4)**	<0·0001
Proportion ≥150 mm Hg	221 (60·9%)	67 (56·3%)	118 (45·7%)	0·0002
Proportion ≥160 mm Hg	185 (51·0%)	48 (40·3%)	69 (26·7%)	<0·0001
Diastolic blood pressure (mm Hg)				
Mean (95% CI) most recent measurement	88·0 (86·7–89·3)¶	87·3 (85·0–89·6)‖	82·0 (80·5–83·5)**	<0·0001
Proportion ≥85 mm Hg	214 (59·0%)	67 (56·3%)	104 (40·3%)	<0·0001
Proportion ≥90 mm Hg	190 (52·3%)	58 (48·7%)	67 (26·0%)	<0·0001
Smoking				
Current	123 (32·6%)††	36 (29·8%)‡	47 (18·1%)††	<0·0001
Ex	147 (37·4%)	42 (34·7%)	96 (36·9%)	
Never	123 (31·3%)	47 (38·8%)	117 (45·0%)	
Diabetes	45 (10·5%)	12 (9·4%)	25 (9·5%)	0·69
Previous transient ischaemic attack	52 (12·1%)	16 (12·5%)	41 (15·6%)	0·19
Known previous atrial fibrillation	41 (9·6%)	17 (13·3%)	44 (16·8%)	0·005
Previous myocardial infarction	78 (18·2%)	14 (10·9%)	33 (12·6%)	0·05
Angina	67 (15·6%)	22 (17·2%)	32 (12·2%)	0·21
Peripheral vascular disease	50 (11·7%)	10 (7·8%)	22 (8·8%)	0·23

*Data are number of patients (%) unless otherwise indicated. *1981-84 vs 2002-04. Unavailable in †76 (17.7%) cases, ‡19 (14.8%), , § 25 (9.5%), ¶66 (15.4%), ‖nine (7.0%), **4(1.5%), ††36(8.1%), ‡‡two(0.8%)*

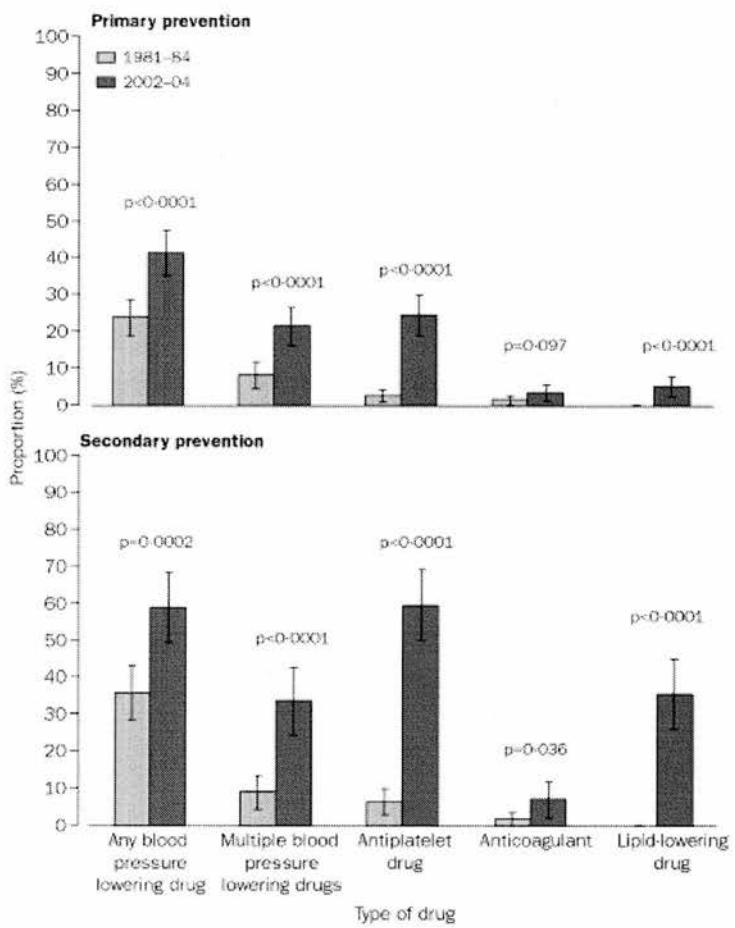
Table 9.5 Premorbid risk factors and medication in patients with incident transient ischaemic attack

	1981–84 (n=87)	1985–86 (n=67)	2002–04 (n=93)	p*
Baseline characteristic				
Male sex	49 (56·3%)	39 (58·2%)	33 (35·5%)	0·005
Mean (SD) age	67·4 (13·2)	69·8 (12·2)	74·1 (13·0)	0·0007
Premorbid medication				
Treated hypertension			43 (46·2%)	
One drug	..	..	17 (18·3%)	..
Two drugs	..	..	17 (18·3%)	..
Three drugs	..	..	9 (9·7%)	..
Antiplatelet agent	4 (4·6%)	1 (1·5%)	35 (37·6%)	<0·0001
Anticoagulant	2 (2·3%)	2 (3·0%)	6 (6·5%)	0·28
Lipid-lowering drug	0 (0%)	1 (1·5%)	20 (21·5%)	<0·0001
Premorbid risk factor				
Total cholesterol (mmol/L)				
Mean (95% CI) baseline concentration	6·91 (6·54–7·28)†	6·86 (6·53–7·19)	5·61 (5·35–5·87)†	<0·0001
Proportion ≥6·0 mmol/L	57 (68·7%)	47 (70·1%)	32 (36·0%)	<0·0001
Systolic blood pressure (mm Hg)				
Mean (95% CI) most recent measurement	159·1 (156·8–164·4)§	153·9 (147·3–160·5)¶	146·5 (141·8–151·1)‖	0·002
Proportion ≥150 mm Hg	53 (67·1%)	40 (61·5%)	41 (44·6%)	0·003
Proportion ≥160 mm Hg	42 (53·2%)	26 (40·0%)	27 (29·3%)	0·002
Diastolic blood pressure (mm Hg)				
Mean (95% CI) most recent measurement	87·4 (84·6–90·2)§	85·3 (82·6–88·0)¶	80·4 (78·0–82·8)‖	0·0002
Proportion ≥85 mm Hg	44 (55·7%)	35 (53·8%)	32 (34·8%)	0·006
Proportion ≥90 mm Hg	37 (46·8%)	29 (44·6%)	23 (25·0%)	0·003
Smoking				
Current	27 (31·0%)	16 (23·9%)	14 (15·1%)	0·03
Ex	34 (39·1%)	33 (49·3%)	39 (41·9%)	
Never	26 (29·9%)	18 (26·9%)	40 (43·0%)	
Diabetes	8 (9·2%)	3 (4·5%)	9 (9·7%)	0·91
Known previous atrial fibrillation	9 (10·3%)	6 (9·0%)	14 (15·1%)	0·34
Previous myocardial infarction	7 (8·1%)	5 (7·5%)	10 (10·8%)	0·53
Angina	13 (14·9%)	18 (26·9%)	14 (15·1%)	0·98
Peripheral vascular disease	8 (9·2%)	10 (14·9%)	6 (6·5%)	0·49

*Data are number of patients (%) unless otherwise indicate *1981-84 vs 2002-04.. †4 cases, ‡ five, § eight, ¶ two, ‖ one.*

A lower frequency of symptomatic arterial disease was recorded in other vascular territories in 2002–04 incident strokes than in 1981–84 (table 9.4). This difference was less obvious in the transient ischaemic attacks (table 9.5) but the OXVASC patients were significantly older. Figure 9.2 shows data for premorbid preventive medication in patients with incident transient ischaemic attacks and with incident stroke combined and stratified according to whether or not the individual had any previous symptomatic vascular disease—ie, primary prevention versus secondary prevention. Secondary prevention patients had a previous transient ischaemic attack (in stroke cases), acute coronary syndrome, angina, or symptomatic peripheral vascular disease.

Fig 9.2 Premorbid medication in patients with incident first-ever transient ischaemic attack or stroke.



9.5. Discussion

We have shown a major reduction in the age and sex specific incidence of stroke in Oxfordshire, UK, over the past 20 years. As a result, the absolute number of strokes has fallen despite a 33% rise in the population older than 75 years of age and improved ascertainment of stroke in elderly people. This decline was associated with increased use of preventive treatment and better control of vascular risk factors.

Hospital-based studies are prone to bias because changes in patterns of referral, admission, or both can significantly distort longitudinal trends, and major international studies of cardiovascular disease, such as MONICA,[11] are confined to populations younger than 75 years, thereby excluding half of all strokes (52% in OXVASC) and the age-group of greatest current interest. OCSP was one of the first population-based studies to measure the incidence of transient ischaemic attack and stroke, and OXVASC has had more rigorous case ascertainment and a higher brain imaging and autopsy rate than any previous population-based stroke incidence study.

Studies of time-trends in disease incidence can be undermined by changes in diagnosis and investigations. To ensure comparability, we used the same criteria as in OCSP, and had diagnosis and inclusion reviewed by both the original OCSP principal neurologist and one of the study neuroradiologists. However, our estimates of the reduction in incidence of stroke are probably conservative because of under-ascertainment of minor stroke in OCSP, particularly in elderly people. The apparent fall in incidence of transient ischaemic attack and minor stroke in elderly patients in OCSP is contrary to all other reliable data, and is highly likely to represent underascertainment.

To quantify exactly the difference in completeness of ascertainment between OXVASC and OCSP is difficult. Indirect statistical modelling methods, such as

capture-recapture, are poorly validated in stroke incidence studies and are unstable or inappropriate in other similar situations.40–42 We therefore used two direct methods to assess completeness of ascertainment in OXVASC, both of which suggested that it was near complete. However, only 84% of incident strokes ascertained in OXVASC were identified by methods that had been used in OCSP. Also, some evidence suggested that the public might now be more likely to seek medical attention after stroke-like symptoms than they were at the time of the OCSP. First, in OCSP, 28 patients were identified who presented with a stroke and who had had a previous incident transient ischaemic attack during the study period but had not sought medical attention.[33]

In OXVASC, only eight such patients were identified (relative proportion 0·60, 95% CI 0·28–1·27). Second, in our large cohort of patients presenting with noncerebrovascular disease (5·5% of our total study population aged more than 60 years) we recorded no patients with symptoms suggestive of transient ischaemic attack or stroke during the study period who had not presented to medical attention. The true reduction in age-specific incidence of stroke between OCSP and OXVASC is best determined with events for which completeness of ascertainment is likely to have been comparable, such as moderately disabling stroke (Rankin 2–3; 39% reduction), major disabling or fatal stroke (Rankin 4–6; 40% reduction), and fatal stroke (37% reduction), the reductions in which were highly consistent. The fall in total anterior circulation ischaemic stroke syndromes was even greater but had wide confidence intervals (35–69%). Some of this reduction might indicate improvements in management of acute stroke since OCSP, but any such effect is likely to have been small for several reasons. First, most stroke patients in Oxfordshire hospitals are still not currently cared for on dedicated stroke units. Second, the number of patients with severe strokes on initial assessment (before treatment), particularly total anterior circulation stroke syndromes and primary intracerebral haemorrhages, suggests a genuine reduction in the incidence of major stroke. Third, a decline in incidence of major stroke is also consistent with the fall in

mortality due to incident fatal stroke in the absence of a reduction in case-fatality of incident stroke.

The 53% reduction in incidence of primary intracerebral haemorrhage confirms the suggestion of a fall of this magnitude in UK mortality and hospital discharge data.[43] A few strokes that did not have brain imaging or autopsy were classified as haemorrhages in OCSP using clinical scoring systems, but this was only done when the score indicated a high degree of certainty.[32] The identification of less clinically obvious haemorrhages due to the higher rate on imaging and autopsy in OXVASC will, if anything, have underestimated the reduction in incidence. A similar fall in the incidence of intracerebral haemorrhage has been reported in Sweden, as well as an increase in minor ischaemic strokes.[44]

We noted major reductions between OXVASC and OCSP in premorbid systolic and diastolic blood pressure, total cholesterol concentration, and smoking. Some data were missing in patients with incident strokes, attributable partly to deaths before assessment, but the results were very similar in patients with transient ischaemic attack, in whom data were virtually complete. The changes do not seem to be due to any systematic change in methods of measurement. Moreover, the measured reductions in blood pressure and cholesterol concentration are consistent with the measured increases in use of blood pressure and cholesterol lowering drugs.

We could not study changes in premorbid risk factors and medication in the whole of our study population, but the findings in patients with incident transient ischaemic attack and stroke are arguably more relevant because they show the changes in a section of the population that was clearly at risk. However, they are likely to underestimate the changes in the at-risk population as a whole because we could not include those patients in whom an incident transient ischaemic attack or stroke was successfully prevented. Nevertheless, our data provide a useful conservative measure of the changes in risk factors and medication in patients at

risk of stroke over the past 20 years. The proportion of the reduction in stroke incidence that is due to these improvements in risk factor control and other preventive treatments is uncertain. Although the changes that we measured, particularly in premorbid blood pressure, are sufficient to account for the reduction in incidence, and might even be expected to produce a greater reduction if representative of changes in the wider at-risk population,[45] we cannot prove that the association is causal and other changes in diet, environment, or behaviour could also be responsible.

The reduction in stroke incidence over the past 20 years should be qualitatively generalisable to other health-care systems that have achieved similar risk factor modification and improvements in preventive treatment. These improvements have been fairly recent in most countries, which could explain why reductions in stroke incidence have not been reported in other studies done in the 1980s and early 1990s.[20–31] The only exception in a population based study is the fall in stroke incidence in Perth, Australia, between 1989–90 and 1995.[46]

Our quantitative findings will be less generalisable to other settings. Even within the UK, mortality due to stroke varies by nearly 50%, with fairly low rates in Oxfordshire. However, nearly all this variation can be accounted for by differences in the frequency of major risk factors,[47] and therefore lends support to our general conclusions. Moreover, the stroke incidence originally reported in OCSP was consistent with other studies of comparable quality elsewhere in Europe, North America, and Australia.[24]

In conclusion, there has been a major reduction in the age-specific and sex-specific incidence of stroke in Oxfordshire, UK, over the past 20 years. Although we cannot prove that the fall in stroke incidence is a direct result of the measured changes in established risk factors, the size of the changes is consistent and the measured increase in use of preventive medication would be expected to produce a significant

reduction in stroke incidence. If the decline in stroke incidence is due in part to risk factor modification and preventive treatment then further reductions are possible with more widespread stroke prevention.

9.6. References

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Chapter 10

What proportion of all acute vascular events in the population are cerebrovascular? Implications for funding of clinical services and research.

10.1. Abstract

Background: In most countries, provision of services for acute assessment, investigation and treatment of TIA and acute stroke is much less than for acute coronary syndromes (ACS). The relative burden of acute cerebrovascular events (TIA, ischaemic stroke, intracerebral and subarachnoid haemorrhage), acute coronary syndrome (ACS) and acute peripheral vascular events (PVE) has never been measured in the same population at the same time. Service provision should be guided both by overall vascular event rates and rates of events that are not immediately fatal and that therefore require investigation, treatment and secondary prevention. We have determined rates of all vascular events in a detailed population-based study.

Methods: The Oxford Vascular Study (OXVASC) is a prospective population-based study of all incident and recurrent acute vascular events in a population of 90,542 in Oxfordshire, UK. All patients attending relevant hospital services and clinics were identified daily and reviewed as soon as possible after the event. All vascular deaths and other relevant events in the community were identified via primary care physicians.

Results: In 18 months we registered 1107 acute vascular events in 773 patients: 434 (27.0%) acute cerebrovascular events (125 TIA, 309 strokes); 586 (36.5%) ACS (67 definite cardiac deaths, 74 probable cardiac deaths including sudden death, 75 STEMI, 168 NSTEMI and 202 unstable angina); 87 (5.4%) acute PVE (52 acute or critical limb ischaemia, 28 acute aortic disease, 6 acute bowel ischaemia and 1 ruptured gastroepiploic artery aneurysm). Most incident TIA and stroke (281, 98.9%) were non-fatal at time of presentation to secondary care compared to 262 (73.1%) ACS and 59 (79.7%) PVE. Crude annual incidence rates were 2.06, 1.93, and 0.43 per 1000 population respectively. Non-fatal first incident accounted for 46.7% of all acute vascular events. Of all 206 incident strokes (179 infarcts, 13 primary intracerebral haemorrhages and 8 subarachnoid haemorrhage), 96.1% had brain imaging or autopsy and 38.2% were managed in outpatients. In total there were 269 incident acute coronary events and 64 incident PVE. Incident strokes accounted for 38.2% of all first-ever acute vascular events. Acute coronary and PVE events accounted for 49.9% and 11.9% respectively. Annually, 1.3% of the over 40 age group had an acute vascular event.

Conclusions: We have documented the relative burden of all acute atherosclerotic disease. Rates of non-fatal acute cerebrovascular and coronary events requiring acute management and secondary prevention are similar. Provision of acute services should reflect this. Cerebrovascular events account for 40% of all acute vascular events in the population. Provision of clinical services and research funding should reflect this.

10.2. Introduction

The burden of a disease is most precisely measured using high quality population-based incidence studies with accurate follow-up of case-fatality and long term outcome.[1] Arterial diseases are the leading cause of death and disability in the developed world, and are rapidly increasing in importance in the developing

world.[2] Although death certificate data may be easily available in some countries they may be inaccurate. Moreover, mortality data are likely to underestimate the overall burden of a disease. Stroke, for example, is the leading cause of neurological disability in the developed world.[3] The detailed burden of all atherosclerotic disease has never been measured in the whole population at the same time. Although the MONICA Project has ongoing studies of both coronary[4] and stroke[5] events, several within the same country, these have not included older patients. Rochester groups have published on both stroke[6] and coronary[7] events in high-quality population-based studies. Individual stroke incidence studies satisfying the Malmgren[8] quality criteria have provided data on stroke burden.[9] There have also been large epidemiological coronary heart disease registers but these have excluded older populations[4,10-12] or have been predominantly hospital-based.[13] There is general agreement however that mortality from coronary heart disease has fallen in developed countries.[14] A similar decline has been seen in mortality from stroke but data remain conflicting and the reasons for the apparent fall in stroke mortality remain unclear.[15] However, there are wide geographical differences with an epidemic of cardiovascular disease emerging in developing countries.[16]

There are no recent UK-based data on the incidence of acute cerebrovascular, coronary and peripheral vascular events. Moreover, there have been major changes over the last 20 years in life-style, primary and secondary prevention treatments, and particularly in population demographics. A formal comparison of incidence and outcome would provide a firm basis on which to guide limited resources for services. Service provision should also reflect rates of events that are not immediately fatal and that therefore require investigation, treatment and secondary prevention.

We have determined both the rates of events non-fatal at time of presentation to secondary care and the overall incidence and case-fatality of all vascular events of any kind in a detailed population-based study.

10.3. Methods

The methods and population for the ascertainment of TIA and stroke were similar to those in the Oxfordshire Community Stroke Project (OCSP, 1981-1986).[17] In brief, between 1st April 2002 and 30th September 2003, we covered a population of 90,542 in nine general practices with 63 Family Practitioners (FP). These practices were all collaborators in OCSP. Patients with TIA and stroke, acute coronary syndrome (ACS), or acute peripheral vascular disease (PVE) (ruptured aortic aneurysms, acute ischaemic limb, acute bowel ischaemia etc) were ascertained prospectively from hospitals and the community. Clinical data was also recorded from patients undergoing elective vascular procedures for atherosclerotic disease (angioplasty, endarterectomy and bypass). Clinical data were obtained retrospectively in those who died in the community and in whom an acute vascular cause was suspected.

In the United Kingdom, patients register with a FP who provides their primary health care and, when necessary, refers them for specialist advice. The FP receives all relevant information about specialist consultations and hospital admissions even if these do not occur locally. Thus the record held by the FP forms a lifelong record of all medical events as well as recording details of each consultation with the FP (including blood pressure recordings, blood counts etc). This individual record is transferred to a new FP if the patient moves residence. The practices that collaborated in the study routinely referred patients to the Oxford Hospitals, had an accurate computerised age-sex register (ASR), were willing to notify us of all acute vascular events and were computerised allowing searches for diagnostic codes. The population was predominantly Caucasian (94%) as well as Asian (3.1%), Chinese (1.5%) and Afro-Caribbean (1.4%) and included the full range of social deprivation.

We used hot and cold pursuit with multiple overlapping sources of ascertainment to ensure complete case finding. Collaborating FPs notified the study office by telephone or facsimile of any patient whom they thought might have had an episode of acute neurological dysfunction caused by cerebrovascular disease. FPs

also informed us of patients who had not been admitted to Oxford Hospitals with an acute vascular event or died before reaching hospital of a suspected vascular event. Patients who had an event whilst temporarily away from Oxford were included, but visitors to Oxford who were not normally resident and registered with a FP were excluded. A liaison FP in each practice checked with colleagues regularly to ensure that all relevant patients were referred. A liaison administrator in each practice assisted in searching computerised records for patients with suspected vascular disease. The study team maintained frequent personal contact with liaison FPs and our research nurse visited each practice at least twice a month. A quarterly newsletter was sent to all collaborators and FPs. A pager was carried by a Study Physician between 8am and 6pm from Monday to Friday.

Patients with TIA or stroke not requiring hospital admission were seen in a daily clinic. Patients were referred from the Oxford Eye Emergency Department if diagnosed with retinal ischaemia. Patients in whom hospital assessment was not possible were assessed in the community by a Study Physician. Computer-generated admission registers and a list of all patients undergoing troponin I measurement (for suspected ACS) for each of the collaborating General Practices were studied daily. The cardiothoracic, coronary care, medical admissions, vascular surgery and acute stroke units were visited daily. The notes of all possible patients were reviewed to identify any cases with acute vascular events. Day case units for patients attending for coronary or peripheral angiography were visited daily. We identified the causes of all hospital deaths.

Practice-specific computer-generated lists of patients admitted to Rehabilitation wards and attending the outpatient clinics of other stroke physicians were reviewed on a weekly basis. We were notified of all patients referred for a vascular surgical opinion, endovascular or vascular surgical intervention.

All referrals for brain and carotid imaging for patients registered with our collaborating FPs were reviewed on a monthly basis for cases of suspected TIA or stroke. Paediatricians and obstetricians were contacted monthly to ascertain patients with acute vascular events occurring in their patients. All relevant patients coded on discharge with ICD-10 acute vascular events or OPCS-4 vascular procedures were identified. Regular visits to the practices and the Coroner's office identified deaths in the community. Cases with an ICD-10 vascular code cause of death were generated and supplied by the local Department of Public Health. FP databases were searched for all patients with a relevant diagnosis in the study period on a regular basis.

The patients were assessed as soon as possible after the event by a study clinician. Patients were assessed in the daily stroke and TIA clinic, in hospital or at home. Informed consent was sought if possible. If the patient was too unwell then relatives were contacted to obtain assent. FP and hospital medical records were reviewed and previous illnesses, premorbid medication and blood pressure measurements were recorded. Relevant FPs were interviewed and all available documentation reviewed to ascertain an accurate cause of death for fatal cases.

Standard definitions of TIA and stroke were used.[18,19] We attempted to get brain and carotid imaging in every TIA and stroke cases and echocardiography if clinically indicated. Diagnoses were confirmed initially with a Consultant Neurologist (PMR) and to ensure comparability with OCSP, by their lead investigator (CPW).

Unstable angina was defined clinically as symptoms of angina at rest, new-onset angina on minimal exertion, or crescendo angina that was clinically more severe, more prolonged or more frequent based on a pre-existing stable pattern[20] resulting in admission to hospital with no rise in cardiac markers of necrosis.

Myocardial infarction was defined in the presence of two of three of an appropriate clinical history, typical ECG changes and raised cardiac enzymes (troponin I or standard cardiac enzymes CK and AST). A Consultant Cardiologist (AB) reviewed diagnoses.

Critical limb ischaemia was defined as a combination of rest pain and / or gangrene in patients often with multi-level arteriopathic disease. An acute peripheral vascular event was defined as any acute vascular catastrophe of any part of the arterial system leading to hospital admission. Consultant Vascular Surgeons caring for the patient confirmed all diagnoses.

Patients were also included in the study if they attended for any endovascular or vascular surgical intervention of the investigation or treatment of atherosclerotic disease.

Survivors of acute vascular events were followed prospectively and interviewed by Research Nurses at 1, 3, 6, and 12 months from the time of their event at home, clinic or hospital. A standardised questionnaire was designed to detect recurrent vascular events. If a recurrent stroke was suspected the patients was reassessed by a study physician. More detailed information on functional ability, activities of daily living, social and psychological functioning were also collected.

For the purpose of this analysis, all patient events have been recorded including follow up vascular interventions, strokes, MI and PVE. Recurrent events were defined as any further vascular event occurring after a prior period of 24 hours stability. Death within 30 days to an acute vascular event was attributed to the initial event. Case-fatality was defined as any death occurring within 30 days of the initial event.

10.4. Results

Between 1st April 2002 and 30th September 2003, 1909 patient events in 1346 patients were considered for inclusion. After careful review 303 were excluded as they failed to meet our diagnostic criteria for vascular events. Of the remaining 1606 patient episodes, there were 434 (27.0%) acute cerebrovascular events, 586 (36.5%) ACS and 87 (5.4%) acute PVE. There were 188 (11.7%) acute endovascular or vascular surgical interventions as a consequence of mainly the acute coronary and peripheral vascular events. The remaining 311 (19.4%) patient episodes were endovascular or surgical interventions performed to investigate atherosclerotic disease (Figure 10.1).

There were 1107 acute vascular events in 773 patients. Of 434 acute cerebrovascular events, there were 125 (28.8%) TIA and 309 (71.2%) strokes. Of 586 ACS, 67 (11.4%) were definite cardiac deaths, 74 (12.6%) probable cardiac deaths including sudden death, 75 (12.8%) ST elevation myocardial infarction (STEMI), 168 (28.7%) non ST elevation myocardial infarction (NSTEMI) and 202 (34.5%) cases of unstable angina. Of 87 PVE, there were 37 (42.5%) episodes of acute limb ischaemia, 28 (32.1%) acute aortic disease (21 abdominal, 7 thoracic), 15 (17.2%) critical limb ischaemia, 6 (10.3%) acute bowel ischaemia and 1 (1.1%) ruptured gastroepiploic artery aneurysm (Figure 1).

Of the 284 first-ever-in-a-lifetime acute TIA and strokes, 281 (98.9%) were non-fatal at time of presentation to hospital or outpatient facilities. Of 358 incident ACS, 262 (73.1%) were non-fatal at time to presentation to secondary care facilities. Of the 74 acute PVE, 59 (79.7%) were non-fatal at time of presentation. The annual incidence rates adjusted for England and Wales population (2001) were 2.34, 2.09, and 0.48 per 1000 population respectively (Figure 10.2).

Figure 10.1. Burden of vascular events in first 18 months of OXVASC

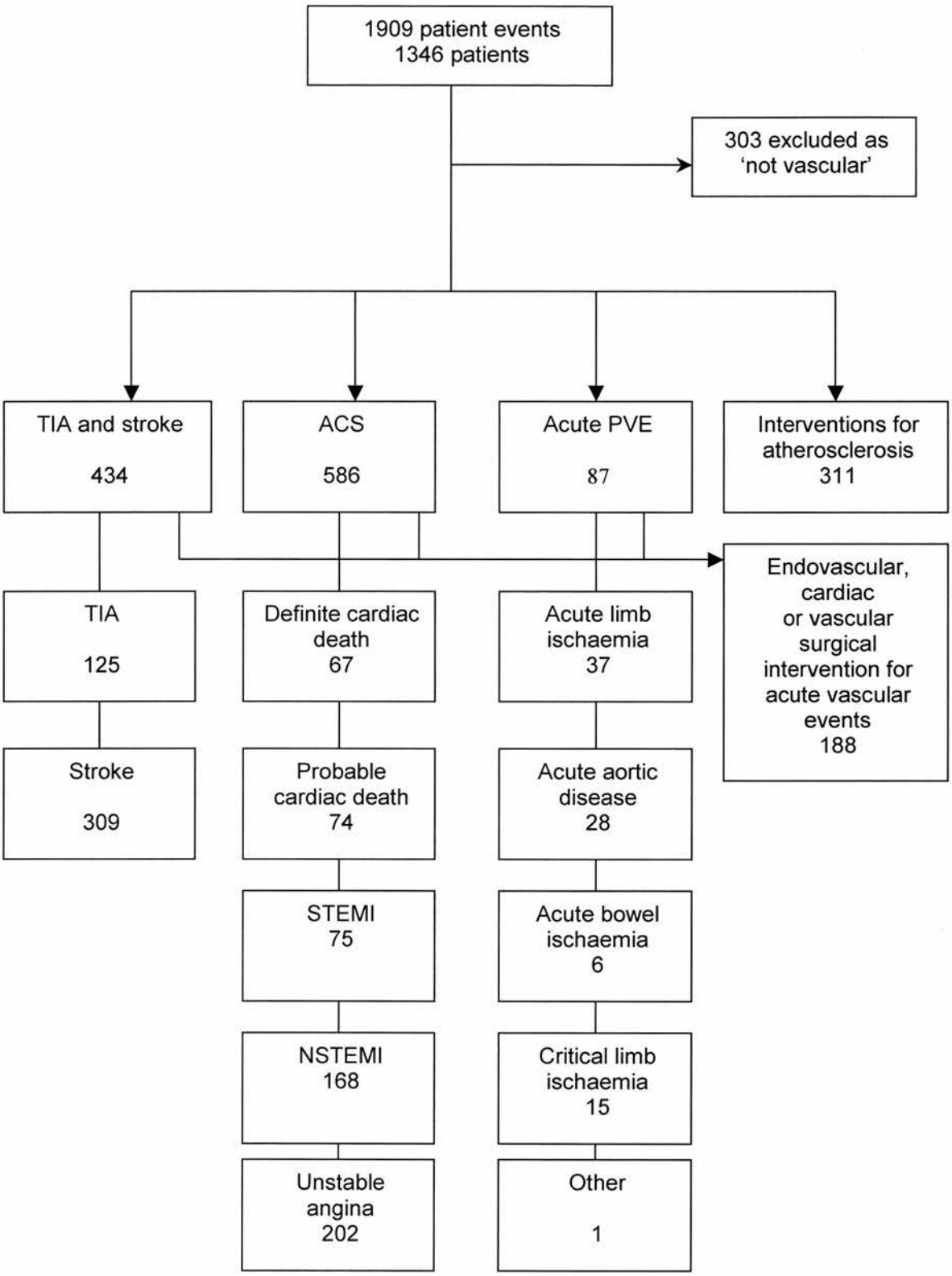
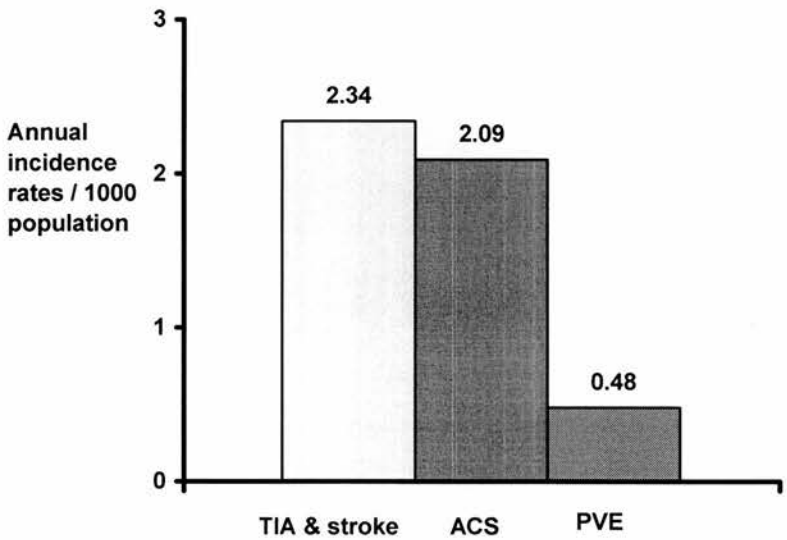


Figure 10.2. Population adjusted annualised / 1000 population rates of non fatal at time of presentation to secondary care of TIA and stroke, ACS and PVE

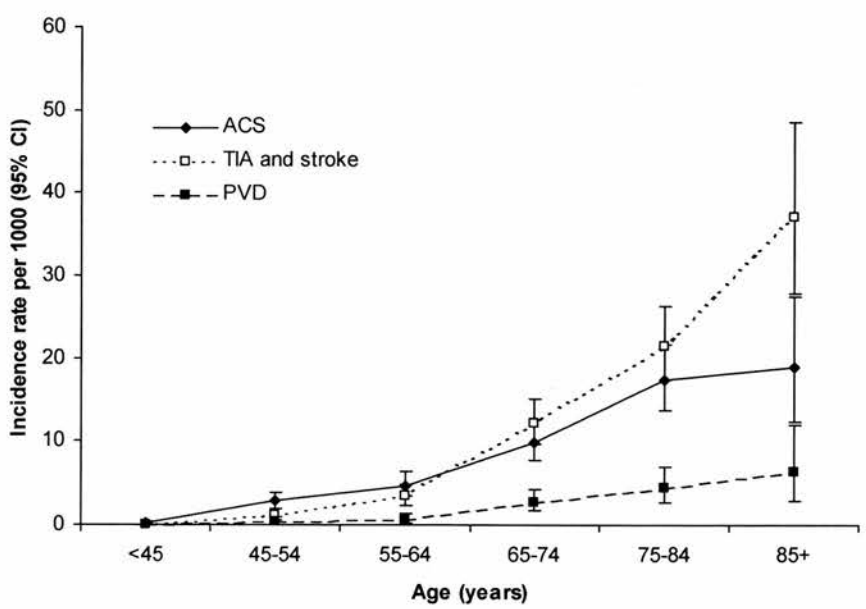


In patients aged ≥ 65 years, the crude annualised rates were rates were 15.44, 9.04 and 2.52 respectively. Non-fatal first ever acute cerebrovascular events accounted for 46.7% of all acute vascular events. Non-fatal incident acute coronary and PVE events account for 43.5% and 9.8% respectively. TIA and stroke became more common than ACS after age 65 (Figure 10.3).

Table 10.1. Adjusted annualised incidence rates of TIA and stroke, ACS and PVE non-fatal at time of presentation to secondary care.

	Adjusted annual incidence rates per 1000 (95% CI) to the population of England & Wales 2001		
	TIA & stroke	ACS	PVE
Males	2.02 (1.66-2.37)	2.59 (2.19-2.98)	0.57 (0.39-0.76)
Females	2.64 (2.22-3.06)	1.62 (1.3-1.94)	0.39 (0.23-0.56)
Overall	2.34 (2.06-2.61)	2.09 (1.84-2.35)	0.48 (0.36-0.60)

Figure 10.3. Age specific incidence rates for non-fatal TIA and stroke, ACS and PVE at time of presentation to secondary care



There were 206 incident strokes with 100 (48.5%) males and a mean age of 74.4 (11.7) years ranging between 38 and 94 years. 82 (39.8%) were managed wholly on an outpatient basis. The combined brain imaging and autopsy rate for incident strokes was 96.1%. There were 179 (86.9%) infarcts, 13 (6.3%) primary intracerebral haemorrhages and 8 (3.9%) subarachnoid haemorrhage. 8 patients had neither brain imaging nor autopsy. The overall age and sex adjusted 30-day case fatality (95% CI) was 11.0% (7.2 – 14.7). It was 8.2% (4.9 - 11.5), 33.7% (13.7 - 53.7), 12.6% (1.8 - 25) for cerebral infarction, PICH and SAH respectively.

There were 269 incident acute coronary events with 175 (65.1%) males and a mean age of 71.8 (13) years ranging between 29 and 98 years. There were 57 (21.1%) STEMI, 113 (42%) NSTEMI, 52 (19.3%) definite cardiac deaths and 47 (17.5%) probable cardiac deaths including sudden deaths. The overall 30-day adjusted case fatality of incident myocardial infarction including out-of-hospital deaths was 32.5%. (26-39). For ACS cases non-fatal at time of presentation, the age and sex adjusted 30 day case fatality rates were 5.7% (3.0 - 8.4). The comparable case fatality for non-fatal incident strokes was 11.9% (8.0 – 15.8).

There were 64 incident PVE, 38 (59.4%) males, mean age 73.6 (14.1) including 32 (50%) acute limb ischaemia, 27 (42.2%) acute aortic pathology, 5 (7.8%) acute ischaemic bowel. Overall age and sex adjusted case fatality was 26.5% (16.1 - 36.9).

Case fatality for different acute vascular events are summarised in Table 10.3. The incidence of ACS increased in parallel with stroke (Figure 10.4). Incident strokes accounted for 38.2% of all incident acute vascular events. Acute coronary and PVE events accounted for 49.9% and 11.9% respectively.

Table 10.2. Adjusted annualised incidence rates of first-ever-in-a-lifetime major acute vascular events - stroke, myocardial infarction (including cardiac and sudden death) and PVE (excluding critical ischaemia)

	Adjusted annual incidence rates per 1000 (95% CI) to the population of England & Wales 2001		
	Stroke	ACS	PVE
Males	1.60 (1.29-1.92)	2.76 (2.35-3.17)	0.61 (0.41-0.8)
Females	1.81 (1.46-2.15)	1.62 (1.29-1.94)	0.45 (0.27-0.62)
Overall	1.71 (1.47-1.94)	2.17 (1.91-2.43)	0.53 (0.4-0.65)

Figure 10.4. Age specific incidence rates of first-ever-in-a-lifetime stroke, ACS and PVE

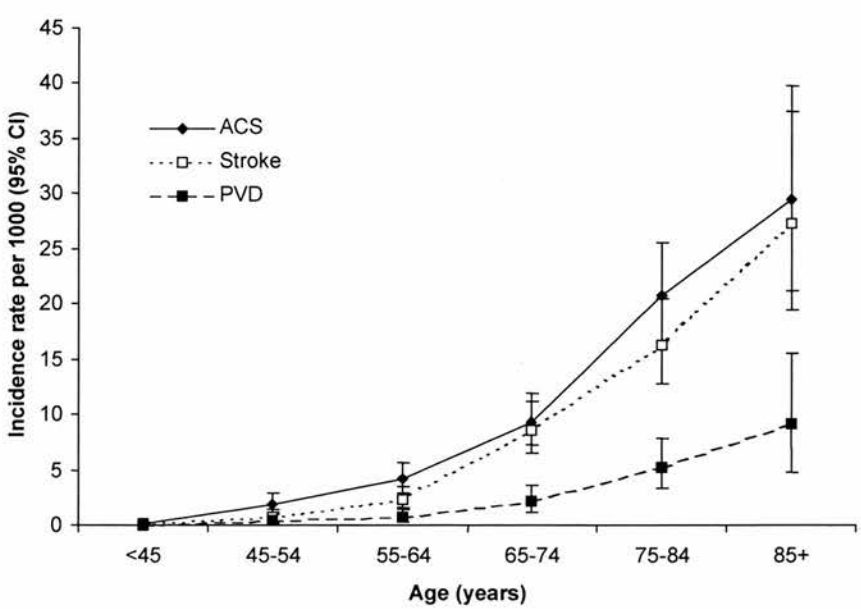


Table 10.3. Age and sex adjusted 30 day case fatality rates for incident stroke, myocardial infarction (including cardiac and sudden death) and PVE (excluding critical ischaemia)

	Adjusted 30 day case fatality rates (%) (95% CI) to the population of England & Wales 2001		
	Stroke	ACS	PVE
Males	8.0 (5.0-12.2)	31.9 (23-40.8)	26.8 (13.2-40.4)
Females	12.8 (7.6-20.2)	33.1 (23.5-42.7)	26.0 (9.9-42.2)
Overall	11.0 (7.2-14.7)	32.5 (26-39)	26.5 (16.1-36.9)

During the 18 months studied there were 1098 acute vascular events in 761 patients over the age of 40 in our population of 90542 (age >= 40, n=39301). Annually, 1.3% of the over 40 age group had an acute vascular event. 1.6% of this age group had an acute vascular event or an endovascular or vascular procedure for the investigation or treatment of atherosclerotic disease.

10.5. Discussion

We have carefully detailed the relative burden of all incident and recurrent, acute and elective atherosclerotic vascular events occurring in a well-defined population in a high quality study. Our results have important implications.

Firstly, we have shown that the burden of incident non-fatal acute cerebrovascular events (TIA and stroke) reaching either hospital or outpatients is similar, if not greater than the number of ACS reaching hospital alive. We have included TIA within this analysis as there is increasing evidence that this should be treated as a

high-risk medical emergency[21, 22] akin to unstable angina. Non-fatal first-ever acute cerebrovascular events accounted for 47% of all acute vascular events and become increasingly more common with age. In contrast to acute cerebrovascular events, a large proportion of ACS die prior to reaching hospital and thus their impact on secondary care is limited. Moreover, the case-fatality for non-fatal acute cerebrovascular events was double that for ACS reaching hospital alive (11.9% vs 5.7%). If all fatal and non-fatal major incident acute vascular events were included, stroke still accounted for 38% of acute events. There is an urgent need for the provision of services for the assessment, investigation and treatment of acute cerebrovascular events that are at least equivalent to that for coronary events.

Secondly, the majority of incident strokes were admitted to hospital in our study with 40% managed wholly in the outpatients considerably lower than the proportion of non-hospitalised strokes in OCSP (59%).[17] There is considerable variation between developed countries in the proportion of incident strokes managed as outpatients ranging from less than 10%[23-25] to 25%.[26] This rise in admission for stroke may reflect a less nihilistic attitude to the management of stroke in the UK. There has also been a realisation of the availability and importance of brain imaging. Our combined brain imaging and autopsy rate of 96.1% is one of the highest amongst quality population-based studies and allowed accurate phenotyping of incident stroke cases.

Thirdly, the overall adjusted 30 day case fatality for incident strokes in our study was 11%, markedly lower than OCSP (19%) done two decades ago. This fall in case fatality is of a greater magnitude of the decline in case fatality reported in other studies in Finland (33%),[27] Japan (26%),[28] Russia (24%)[29] and Auckland (16%).[30] Other groups in Perth[31] and Rochester[6] have not shown a fall in case-fatality. The first year results from OXVASC have also shown a decrease in stroke incidence particularly in severe strokes, (See Chapter 9) and these results together would suggest that the decline in stroke mortality is associated with the greater recognition

of more minor strokes and the reduction in incidence of severe stroke. These are likely to be related to the consequence of blood pressure and cholesterol lowering treatment. More minor strokes and the fall in severe strokes have lead to a fall in case fatality. It may be that the latter is also associated with improved acute stroke care in hospital.

Finally, our results confirm the heavy burden of atherosclerotic disease. Annually, more than 1 in 100 (1.3%) patients in our population over the age of 40 had an acute vascular event. 1.6% of this age group had an acute vascular event or needed an endovascular or vascular procedure for the investigation or treatment of atherosclerotic disease. The implications for resource provision in terms of both primary and secondary care for assessment, investigation and secondary prevention of this group are huge.

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There are some potential problems with our study. In our analysis of non-fatal stroke cases we included any patient who reached hospital alive even though they may have died within 24 hours. There were 15 cases that died within 24 hours. However, even if these were excluded from the burden analysis, non-fatal acute cerebrovascular events would still have accounted for 45.6% of acute vascular events. Death certification has inherent potential inaccuracies. However, we have used all available data including FP records, post mortem reports and coding data provided by the Department of Public Health to confirm cause of death. We also had a close collaboration with FPs and discussed difficult cases of sudden death were cause was unclear. The relatively low yield of acute stroke from death certificates confirms the increasing knowledge that stroke is rarely a cause of sudden death[32] and the increased hospitalisation of patients with suspected stroke.

10.6. Conclusions

We have presented detailed information on the relative burden of all acute vascular events. This provides evidence for a real need to properly resource the clinical

management of acute cerebrovascular events. It also highlights the importance of redressing the considerable imbalance in clinical and research funding between stroke and MI.[33] Further research will be required to assess the disability and long term outcome associated with different atherosclerotic diseases.

10.7. References

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Chapter 11

Conclusions

11.1. Introduction

The Oxford Vascular Study aims to study the incidence, outcome and long term sequelae of all atherosclerotic events in the same population at the same time. This thesis has aimed to introduce the reasons behind setting up this important study and the methods that have been used. I have presented results from data collected from the first 18 months of the study with particular emphasis to acute cerebrovascular disease. There is a great deal more data, including that collected for ACS and PVE, that will provide further excellent research opportunities in the future.

11.2. Case definition

I have also examined the effect of case definition on measured stroke incidence rates (see Chapter 4). Case definition for stroke is not uniform and there are subtle but perhaps important differences. These differences are unlikely to have a major impact on incidence but there remains a strong case for clarity in the presentation of

inclusion and exclusion criteria. Moreover, there is a real need to assess and follow-up cases of 'possible TIA' or 'possible stroke' as the comparison of the prognosis of these events with other definite events may often be the best (and only) guide to the nature of the initial diagnosis. It is these data that can often be so important in guiding further clinical practice. We have been collecting these 'possible' cases and we hope once we have sufficient numbers that we can make real progress in defining these events more clearly.

11.3. Case ascertainment

Although I have presented only a small part of the available data for analysis, one of the specific aims of the first year was to ensure that case ascertainment was reliable and complete. This study was only possible because of the important contribution of our collaborating GPs. We have been able to show that our ascertainment was near complete using our multiple overlapping sources of ascertainment (see Chapter 5). Moreover, we have used a novel method of direct assessment of ascertainment by interviewing patients with other vascular disease at high risk of further vascular events to try and ascertain acute cerebrovascular events. Despite interviewing more than 5% of the at risk population of our practices, we found no TIA or strokes that we had not ascertained through other methods already.

11.4. Capture - recapture

There has been a great deal of interest in the application of capture-recapture techniques[1] to stroke incidence studies to assess completeness of ascertainment (see Chapter 5). We feel there is now an excellent opportunity to assess the validity of this technique in a population where other methods have ensured near complete ascertainment so the number of strokes is actually known. We plan to use the capture-recapture model on our data using different methods of ascertainment and various covariates to assess this technique further.

11.5. Further research

We have collected detailed data (see Chapter 3) on a large number of patients with actue vascular events and those attending for elective endovascular or vascular surgical procedures. There remains a great deal of data to be analysed on many areas including triggers for vascular events, life events, dietary habit, sleep disorder, cognition and mood disorder. Once larger numbers have been enrolled into the study, it is hoped that it will be possible to compare between acute vascular events and to register community case controls from the collaborating practices. The collection of premorbid data including blood pressures, lipids and other biochemical and haematological markers will provide an exciting resource for further study. Moreover, the collection and storage of blood from actue vascular cases will allow further study of novel risk factors that may be discovered in the future.

11.6. The daily clinic and the early risk of recurrence

Our daily rapid access TIA and minor stroke clinic has provided an important clinical service to our collaborating GPs as well as providing an excellent vehicle for research. This clinic sees a wide variety of cases with many neurological and general medical diagnoses (see chapter 4). It is also clear that only through this type of research is it possible to really measure the high early risk of recurrence after TIA or minor stroke (see Chapter 7). Further study has shown that the patients most at risk are those with large artery disease (see Chapter 8). We have also shown that the early risk of recurrence after stroke can be falsely low if the definition of recurrence is restrictive (see Chapter 6). Data from OXVASC and OCSP[2] needs to be analysed to determine the risk of neurological deterioration within the first 24 hours of their initial event.

11.7. The further development of the daily 'clinic'

There is a real need from a service perspective to continue providing patients with rapid expert assessment after their TIA or stroke, with early if not same day brain

imaging, and the urgent need to address the aetiology of their event with carotid or cardiac imaging. In the near future we plan to start admitting patients referred by our collaborating practices with TIA or stroke for urgent assessment, brain imaging with MRI including diffusion weighted sequences and CT angiography to image both the arch of aorta and carotid system both extracranial and intracranial. With this detailed information, we would hope to treat patients more aggressively potentially with early anti-platelet therapy, statins and ACE inhibitors if appropriate. By comparing these cases with those registered in the first two years of the study, there may be the power to show a benefit in the reduction of risk of early recurrence after TIA or minor stroke.

There has been considerable debate regarding the diagnosis of TIA in the context of infarction on brain imaging.[3] With the above rapid assessment and brain imaging protocols we should be able to add to this debate with detailed, well phenotyped population-based data. Moreover, it will be potentially possible to more accurately define the aetiology of stroke by using the existing TOAST[4] classsification or developing other classifications based on the results of further study.

11.8. Incidence and time trends in TIA and stroke

We have shown a marked reduction in the incidence of stroke since OCSP using comparable methods particularly in severe stroke (see Chapter 9). We have also shown an increase in TIA but this is likely to be explained by a more informed public and medical profession as well as better ascertainment. Alongside this we have shown the increase in use of anti-platelet therapy, blood pressure lowering and cholesterol lowering treatment and a reduction in the mean systolic and diastolic blood pressure cholesterol level since the 1980s. There has also been an important decline in case fatality. These results should be however treated with caution. They represent data from only the first year of study and numbers are small, and although the differences that have occurred over the last 20 years are highly

statistically significant, we should await more results over a longer time period with greater numbers.

11.9. Burden of vascular disease

OXVASC has also provided preliminary population-based data on the epidemiology of the other acute vascular events. There are few high quality population-based studies studying the burden of acute peripheral vascular disease. Moreover, studies of coronary disease have often excluded more elderly groups. In preliminary data presented in this thesis (see chapter 10), we have shown the continued increasing incidence of myocardial infarction in parallel to stroke with age. This is an important result in coronary heart disease epidemiology and requires further study.

11.10. Conclusions

The burden of atherosclerotic disease is huge (see Chapter 10). OXVASC has and will provide high quality up-to-date information for politicians, service providers and clinicians to help guide the prioritisation of limited resources to best fit the needs of the population. Future study of this population-based cohort will allow the comparion and measurement of the burden of long-term disability in this large group of patients.

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Appendices

Appendix 1 List of collaborating GP practices

Name of General Practice	Liaison GP	Liaison Administrator
19 Beaumont Street, Oxford. OX1 2NA	Dr Meriel Raine	Angie Eachus
East Oxford Health Centre, Manzil Way, Oxford. OX4 1XD	Dr Tom Nicholson-Lailey	Maggie Perrin
Berinsfield Health Centre, Fane Drive, Berinsfield. OX10 7NE	Dr Henry Hoy	Sandy Weatherall
The Malthouse Surgery, The Charter, Abingdon. OX14 3JY	Dr David Otterburn	Peter Avery Liz Talbot
Exeter Surgery, Exeter Close, Kidlington. OX5 1AP	Dr Simon Street	Caroline Jones
Kidlington & Yarnton Medical Group, Exeter Close, Kidlington. OX5 1AP	Dr David Evans	Richard Merrill
Church Street Practice, Mably Way, Wantage. OX12 9BN	Dr Mark Drury	Sheila Dearman
Marcham Road Family Health Centre, Marcham Road, Abingdon. OX14 1BT	Dr Michael Robertson	Rose Moore
The Abingdon Surgery, 65 Stert Street, Abingdon. OX14 3LB	Dr Pridip Buttar	Theresa Young

Appendix 2 Age and sex register for study practices

(Figures exclude armed forces and prisoners)

Total practice population by age/sex as at 1 January 2002

K84 code	Senior Partner		00-04	05-09	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Totals
K84023	**Agass M**	Males	155	191	212	150	110	144	194	269	197	167	148	193	159	127	108	70	41	30	2665
	(Berinsfield)	Females	155	168	171	134	95	138	213	207	185	140	173	191	148	123	107	76	73	93	2590
		Totals	310	359	383	284	205	282	407	476	382	307	321	384	307	250	215	146	114	123	5255
K84033	**Bryan P**	Males	327	377	396	342	280	331	406	479	487	435	449	358	286	282	221	198	110	66	5830
	(Church St Prac	Females	320	364	450	432	280	312	410	458	511	397	391	381	307	278	259	243	199	196	6188
	Wantage)	Totals	647	741	846	774	560	643	816	937	998	832	840	739	593	560	480	441	309	262	12018
K84054	**Cave R**	Males	246	292	298	274	296	402	407	458	421	358	367	346	284	234	173	132	77	52	5117
	(Stert St Surgery	Females	232	279	308	290	280	331	371	403	392	311	354	299	245	221	188	170	130	99	4903
	Abingdon)	Totals	478	571	606	564	576	733	778	861	813	669	721	645	529	455	361	302	207	151	10020
K84027	**Dugdale-Debney F**	Males	534	651	877	1114	625	675	747	783	698	686	739	677	532	433	440	345	205	111	10872
	(Malthouse Surg	Females	534	554	606	512	571	655	719	673	658	628	695	644	465	495	455	437	338	258	9897
	Abingdon)	Totals	1068	1205	1483	1626	1196	1330	1466	1456	1356	1314	1434	1321	997	928	895	782	543	369	20769
K84016	**Maclennan DN**	Males	177	163	157	638	1749	970	708	604	401	322	250	218	125	116	100	85	43	39	6865
	(19 Beaumont St)	Females	164	159	159	547	1304	663	449	314	247	230	198	176	142	91	97	107	59	72	5178
		Totals	341	322	316	1185	3053	1633	1157	918	648	552	448	394	267	207	197	192	102	111	12043
K84032	**Stein TR**	Males	229	244	251	230	260	422	442	437	291	258	254	182	210	182	131	111	44	37	4215
	(East Oxford HC)	Females	235	255	219	233	256	344	319	280	220	198	181	190	154	126	115	94	63	70	3552
		Totals	464	499	470	463	516	766	761	717	511	456	435	372	364	308	246	205	107	107	7767
K84022	**Street SH**	Males	240	299	343	313	406	371	346	460	400	397	403	257	208	198	179	106	67	51	5044
	(Kidlington HC)	Females	245	301	369	323	282	255	324	428	385	392	342	269	237	219	192	164	126	110	4963
		Totals	485	600	712	636	688	626	670	888	785	789	745	526	445	417	371	270	193	161	10007
K84041	**Tate PHL**	Males	410	435	413	381	365	398	497	511	505	437	498	435	328	287	192	140	83	45	6360
	(Marcham Rd Prac	Females	395	415	383	356	341	396	488	510	489	440	507	407	319	254	215	165	126	97	6303
	Abingdon)	Totals	805	850	796	737	706	794	985	1021	994	877	1005	842	647	541	407	305	209	142	12663

Appendix 3 GP 'K84' codes

19 Beaumont Street	K84016
East Oxford Health Centre	K84032
Berinsfield Health Centre	K84023
The Malthouse Surgery	K84027
Exeter Health Centre	K84022
Kidlington & Yarnton Medical Group	K84082
Church Street Practice	K84033
Marcham Road Family Health Centre	K84041
The Abingdon Surgery	K84054

Appendix 4 ICD-10 and OPCS-4 codes

ICD-10 Cerebrovascular disease

G450- G468	Vascular brain syndromes
H340 – H342	Retinal artery ischaemia
H348	Retinal vascular occlusions
I600 – I609	Subarachnoid haemorrhage
I610 – I619	Intracerebral haemorrhage
I620 – I629	Other intracrainial haemorrhages
I630 – I64X	Cerebral infarction – stroke non specified
I650 – I670	Cerebral artery occlusion and dissection of cerebral arteries
I671 – I698	Acute and chronic cerebrrovascular diseases

ICD-10 Ischaemic Heart Disease

I200 – I209	Angina or unstable angina
I210 – I 469	Myocardial infarction, complications or atherosclerotic cardiovascular disease

ICD-10 Peripheral Vascular Disease

I700 – I798	All peripheral vascular disease, aortic disease

OPCS-4 Codes for vascular intervention

A052 – A419	Evac haematoma temp lobe brain - Drainage of subdural
K401 – K489	Coronary artery bypass surgery
K491 – K659	Coronary angiography and intervention
L161 – L269	Aortic surgery
L291 – L359	Carotid and cerebral artery procedures
L411 – L721	Peripheral arterial surgery or endovascular intervention
X073 – X129	Amputations

Specific Oxford Eye Hospital Codes

51	Ischaemic optic neuropathy
63	Arterial occlusion
71	Ocular TIA
98	Visual loss unknown cause

Appendix 5 ICD-10 codes for deaths from vascular events

I602	Cerebral diseases
I609	Cerebral diseases
I619	Cerebral diseases
I620	Cerebral diseases
I629	Cerebral diseases
I633	Cerebral diseases
I639	Cerebral diseases
I64	Cerebral diseases
I679	Cerebral diseases
I694	Cerebral diseases
I698	Cerebral diseases
I219	Ischaemic heart disease
I251	Ischaemic heart disease
I249	Ischaemic heart disease
I259	Ischaemic heart disease
I710	Diseases of arteries, arterioles and capillaries
I711	Diseases of arteries, arterioles and capillaries
I713	Diseases of arteries, arterioles and capillaries
I714	Diseases of arteries, arterioles and capillaries
I718	Diseases of arteries, arterioles and capillaries
I723	Diseases of arteries, arterioles and capillaries
I739	Diseases of arteries, arterioles and capillaries

Appendix 6 Invitation letter to ACS cases ascertained late

Dear

We are a group of researchers based in the Radcliffe Infirmary working closely with your General Practice. We are carrying out a research study called the Oxford Vascular Study (OXVASC). We hope you may be able to help us with this important study. We understand from [GP] that you may have had some heart problems in the recent past. Our study aims to find out how common heart problems are in Oxfordshire and to try and explain the reasons for the changes in the frequency of this common disease over the last twenty years. We hope that the information will help to reduce the risk for other people in the future.

The study involves an interview to ask a few questions about any previous medical problems that you may have had. It also involves gathering information about risk factors from both your hospital and GP notes. We have enclosed a copy of our information sheet. It is entirely voluntary. We would be pleased to answer any questions that you may have. Please telephone 01865 228642 during working hours or leave a message on our 24 hour OXVASC line on 01865 224132 leaving a contact telephone number and we can get back in touch with you.

We will contact you within the next month to ensure you have received this letter. If you would be willing to help telephone either of the numbers above and we will contact you to arrange a convenient time. We would be happy to interview you in your home, our clinic or another place of your choice.

We hope to hear from you.

Yours sincerely

Dr Andrew Coull
Clinical Research Fellow
On behalf of the Oxford Vascular Study

Appendix 7 Invitation letter to relatives in event of patients death

Dear

I am very sorry to trouble you so soon after the death of your spouse / relative. We understand from [GP] that your [spouse / relative] may have died in the recent past and the cause of death may have been related to disease of the blood vessels such as heart attack or stroke. We are carrying out a research study called the Oxford Vascular Study (OXVASC) and we hope you may be able to help us with this important study of how common these problems are in Oxfordshire. The study is done in collaboration with your General Practice and will try to explain the reasons for the changes in the frequency of these common diseases over the last twenty years. We hope that the information will help to reduce the risk for other people in the future.

The study involves an interview to ask a few questions about any previous medical problems that your [spouse / relative] may have had. It also involves gathering more information from both hospital and GP records. We have enclosed a copy of our information sheet.

We would be pleased to answer any questions that you may have. Please telephone 01865 228642 during working hours or leave a message on our 24 hour OXVASC line on 01865 224132 leaving a contact telephone number and we can get back in touch with you.

We will contact you within the next month to ensure you have received this letter. If you would be willing to help telephone either of the numbers above and we will contact you to arrange a convenient time. We would be happy to interview you by telephone, in your home, our clinic or another place of your choice.

We hope to hear from you.

Yours sincerely
Dr Andrew Coull
Clinical Research Fellow
On behalf of the Oxford Vascular Study

Appendix 8 Information sheet

UNIVERSITY OF OXFORD

Oxford Radcliffe Hospitals NHS Trust

The Stroke Prevention Research Unit
Department of Clinical Neurology
Radcliffe Infirmary
Woodstock Road
Oxford 0X2 6HE

Department of Primary Health Care
Institute of Health Sciences
Old Road
Headington
Oxford OX3 7LF

OXREC: CO2.043

AQREC: A02.021

OXFORD VASCULAR STUDY (OXVASC)

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information. Ask us if anything is not clear or if you would like more information.

The purpose of this study is to find out how common vascular disease (e.g. heart attacks, strokes, transient ischaemic attacks and other circulatory problems) is in Oxfordshire and how it affects people's lives. This has never been done before for different types of vascular disease at the same time and in the same population. We hope the study will provide us with useful information on the best way of providing a service for those who suffer from these common problems. We hope we can build up a detailed picture of the way that people recover and the subsequent changes in health over one year.

There is no obligation to take part in the study and your normal care will not be affected in any way whether or not you participate. If you decide to take part you would be given this information sheet and asked to sign a consent form. You are free to withdraw at any time and without giving a reason.

If you decide to take part you would agree to an interview and a clinical examination by the researcher. It would also involve an extra blood test in the hospital or clinic. We would also like to gather some information on risk factors for vascular disease from both your hospital and GP notes. The study would also involve being followed up by telephone or at home by a researcher in thirty days time and at three monthly intervals during the next year. All the information collected will be completely confidential. No investigations, new drugs or other treatments will be tested.

This study is being co-ordinated by the Stroke Prevention Research Unit in collaboration with the Department of Primary Health Care, the Department of Cardiology and your participating General Practice. The local ethics committee has approved the study. The results will be published in medical journals after analysis.

If you would like any further information please ask the researcher who is discussing this information sheet with you.

Thank you for reading this.

Appendix 9 Consent

UNIVERSITY OF OXFORD

Oxford Radcliffe Hospitals NHS Trust

The Stroke Prevention Research Unit
Department of Clinical Neurology
Radcliffe Infirmary
Woodstock Road
Oxford 0X2 6HE

Department of Primary Health Care
Institute of Health Sciences
Old Road
Headington
Oxford OX3 7LF

OXREC: CO2.043

AQREC: A02.021

CONSENT FORM

Title of Project: **OXFORD VASCULAR STUDY (OXVASC)**

Name of Researchers: Dr Peter Rothwell, Dr Andrew Coull, Louise Silver, Linda Bull, Dr Matthew Giles, Mr Jack Fairhead, Dr Ursula Schulz, Dr Enrico Flossmann, Dr Andrew Farmer, Sarah Welch, Dr Cath Sackley and Jo Copley.

Please initial box

1. I confirm that I have read and understand the information sheet dated for the above study and have had the opportunity to ask questions. ☐
2. I agree to take part in the above study. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the follow up study that involves being interviewed at home or a place of my choice, by telephone or in person at 1, 6 and 12 months. ☐
5. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

Name of Patient	Date	Signature
Name of Witness	Date	Signature
Researcher	Date	Signature

Copies: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 10 Assent

UNIVERSITY OF OXFORD

Oxford Radcliffe Hospitals NHS Trust

The Stroke Prevention Research Unit
Department of Clinical Neurology
Radcliffe Infirmary
Woodstock Road
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Department of Primary Health Care
Institute of Health Sciences
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ASSENT FORM

Title of Project: OXFORD VASCULAR STUDY (OXVASC)

Name of Researchers: Dr Peter Rothwell, Dr Andrew Coull, Louise Silver, Linda Bull, Sarah Welch, Dr Matthew Giles, Mr Jack Fairhead, Dr Ursula Schulz, Dr Enrico Flossmann, Dr Andrew Farmer, Dr Cath Sackley and Jo Copley.

Please initial box

1. I confirm that I have read and understand the information sheet dated for the above study and have had the opportunity to ask questions. ☐

2. I understand that the participation of my relative is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected. ☐

3. I understand that sections of any of my relative's medical notes may be looked at by responsible individuals where it is relevant to taking part in research. I give assent for these individuals to have access to my records ☐

4. I agree for my relative to take part in the above study. ☐

Name of Next of Kin	Date	Signature
Researcher	Date	Signature

Copies: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 11 TIA and stroke data collection form (page 1)

ID NO:
Patient identification label

Telephone

Next of kin / contact / relationship
Address

Telephone NOK

Consultant

Examiner

GP Details

Beaumont street	01	East Oxford	03	Berinsfield	04
Malthouse	05	Kidlington	06	Wantage	07
Marcham Rd	08	Stert street	09	Other	10

Summary diagnosis
1. Stroke 2. TIA

3. Amaurosis fugax 4. Retinal artery occlusion
5. Non TIA / stroke –specify

Is this the first ever in a lifetime (incident) stroke? Y / N / U

Is this the first ever in a lifetime (incident) TIA? Y / N / U

Date of notification event
Event leading to notification
Location of interview:
1=JRH in patient / 2=RI in patient / 3=community hospital / 4=outpatients / 5=home / 6=other (specify)

Follow-up plan at 1 month
1=RI TIA clinic / 2=ACS-Primary Care / 3=Refused follow-up / 4=other/ 5=CVA-Primary Care

Information on form obtained from 1=patient / 2=relative / 3=GP / 4=hospital records / 5=death certificate / 6=other

Source of first notification GP=1 / JRH admissions=2 / other hospital=3 / other referrals=4 / health authority search=5 / death=6 / troponin=7/other=9

Other sources of notification(include 1st 2. 3. 4.
Please specify
If one had not identified the patient via the route of first notification would patient been identified by other source of ascertainment? Y / N

Appendix 11 TIA and stroke data collection form (page 2)

Narrative history & examination

Notification event date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
(The event that led to GP notification)

What did you think was wrong?

Were you alone? Y / N ☐

If you were with someone who was it? ☐

Who called for help? ☐

If you did not call for help at time of event, why not?

Who did you (or person with you) first call for help? 1=medical / 2=non medical ☐

First call for help date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
(if medical code '9s')

First call to GP / A&E date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
/ 999 i.e medical

Outcome of first call for medical assistance

Seen by GP / A&E date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐

GP notification to date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
OXVASC/ascertainment

Admission (if admitted) date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐

Assessment date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐

Appendix 11 TIA and stroke data collection form (page 3)

Duration of symptoms (if TIA in minutes) ☐

If onset on wakening from sleep Y / N ☐ time awake ☐

Activity at onset (within two hour of onset)
Estimated no. of met: asleep (1 met); sedentary (2 met); mild-mod activity (3-5 met); strenuous (>6 met) *(need list)* ☐

What were you doing in the same 2 hours on the day prior to the event? Estimated no. of met: asleep (1 met); sedentary (2 met); mild-mod activity (3-5 met); strenuous (>6 met) *(need list)* ☐

Exact circumstances at time of onset of event Y / N

Standing ☐ Sitting ☐ Lying down ☐

Drugs within previous1 hour ☐ Meal within previous one hour ☐

Record exact activity ☐

Location of event ☐

Was there a further event between notification event and assessment? Y / N ☐

Number of events between notification event (event that led to referral) and seeing GP / other medical opinion (Include notification event) ☐

Number of events between seeing GP and notification by GP to OXVASC ☐

Number of events between notification by GP and OXVASC assessment ☐

Were there any events in the month preceding the notification event? Y / N ☐

How many events in the since 1st April before notification event? ☐

Has this patient had a 'high early risk'? Y / N
i.e >= 2 events between notification event and OXVASC assessment or within study period ☐

Total number of events since 1st April 2002
(Include notification event) ☐

Appendix 11 TIA and stroke data collection form (page 4)

History of events between notification and assessment (use extra piece of paper if necessary). Please also describe any events prior to event that led to notification (after 1/4/02).

Date and description of further event

Date and description of further event

Date and description of further event

If admitted (use yellow ambulance sheet)

Arrival of emergency service date time

Arrival in hospital date time
(If not on ambulance sheet use blue admissions)

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	NSTEMI or STEMI	Cerebral TIA CVA	Peripheral
Number of events			
Date of most recent			

Appendix 11 TIA and stroke data collection form (page 5)

Calculated times

Delay from onset of symptoms to call for help

Delay from call for help to arrival ambulance / GP OPD

Delay from call for help to arrival hospital / GP

Were there any event(s) between 1st April 2002 and notification event? Y/N

If YES fill in table below (include notification event)

Previous stroke or TIA Since 1/4/02		date recent	previous yes	previous no	no of events	date 1st event	duration recent	duration longest
Hemispheric stroke carotid	right						xxx	xxxxx
	left						xxx	xxxxx
Hemisheric TIA carotid	right							
	left							
Vertebrobasilar stroke							xxx	xxxxx
Vertebrobasilar TIA								
Stroke unknown territory							xxx	xxxxx
TIA unknown territory								
Amaurosis fugax	right							
	left							
Retinal infarction	right						xxx	xxxxx
	Left						xxx	xxxx

Appendix 11 TIA and stroke data collection form (page 6)

Background Medical History

Angina Y / N ☐ Age at diagnosis ☐

Hypertension Y / N ☐ Age at diagnosis ☐

Myocardial infarction Y / N ☐ Age at diagnosis ☐

Diabetes mellitus Y / N ☐ Age at diagnosis ☐

Treatment: Diet ☐ Tablets Y / N ☐

Insulin Y / N ☐

Valvular heart disease Y / N ☐ Age at diagnosis ☐

Nature: ☐

Intermittent claudication Y / N ☐ Age at diagnosis ☐

Peripheral vascular intervention

Y / N ☐ Age at first intervention ☐

Site:

Type: angiogram ☐ angioplasty ☐ bypass ☐ amputation ☐

Result ☐

Atrial fibrillation Y / N ☐ Age at dia ☐

1=Current / 2=Previous ☐

1=Cardioversion, 2=paroxsymal, 3=persistent, 4=permanent ☐

Pacemaker Y / N ☐ Type ☐

Hyperlipidaemia Y / N / DK ☐ Age at diagnosis ☐

Treatment: Diet Y / N ☐ Statin Y / N ☐ Other ☐

Cardiac failure Y / N ☐ Age at diagnosis ☐ Treated ☐

Appendix 11 TIA and stroke data collection form (page 7)

Migraine Y / N

With aura Y / N

Prolonged aura (>1h) Y / N

Epilepsy Y / N Age at diagnosis

Cardiac intervention Y / N age at first interventic

Angiogram angioplasty stent bypass

Result angiogram
LM / LAD / LCx / RCA
Mild < 50%
Moderate 51–59%
Severe >60%
Bypass grafts

Carotid endarterectomy Y / N Age at operation Side

Asthma Y / N
COAD Y / N

Liver disease Y / N
Peptic ulcer disease

Any previous venous thromboses Y / N No.
Give details below

Any other past medical history

SLE (look in notes) Y / N Age of diagnosis

Anticardiolipin antibodies (aCL) Y / N / DK

Lupus anticoagulant (LA) Y / N / DK

Appendix 11 TIA and stroke data collection form (page 8)

Autoimmune disease Y / N
If so give diagnosis:

Allergies

Nosebleeds Y / N

Bleeding after dental extraction Y / N

Any cancer

End stage renal failure / dialysis

List of medications before onset of notification event

Aspirin Y / N Dose

Dipyridamole Y / N

Clopidogrel Y / N

Warfarin Y / N INR

Aspirin Resistance (ask re drugs in 10 days prior to assessment)

Were you on aspirin before this event? Y/N Date started?

Have you had aspirin since this acute event? Y/N

What doses? (date & dose)

Were you on clopidogrel before this event? Y / N Date started?

Have you had clopidogrel since this acute event? Y / N

What doses? (date & dose)

Have you had any anti inflammatories in 10 days prior to assessment? Y / N

What drug and doses?

Do you take vitamin supplements? Y / N

B6 Y / N FOLATE Y / N B12 Y / N

Appendix 11 TIA and stroke data collection form (page 9)

List names of supplements

Other medication : *scroll of other drugs on database*

Was your BP measured at any time prior to the notification event? ☐

Date of most recent BP measurement prior to notification event ☐

How many times have you had your BP measured in the last year? ☐

Over the last 10 years how many times have you had your BP measured? 1=none, 2=one to two times, 3=three to five times, 4=more than five times, 9=don't know ☐

Previous stroke or TIA Since 1/4/02		date recent	previous yes	previous no	no of events	date 1st event	duration recent	duration longest
Hemispheric stroke carotid	right						xxx	xxxxx
	left						xxx	xxxxx
Hemisheric TIA carotid	right							
	left							
Vertebrobasilar stroke							xxx	xxxxx
Vertebrobasilar TIA								
Stroke unknown territory							xxx	xxxxx
TIA unknown territory								
Amaurosis fugax	right							
	left							
Retinal infarction	right						xxx	xxxxx
	Left						xxx	xxxx

Appendix 11 TIA and stroke data collection form (page 10)

FAMILY HISTORY	dad	mum	sib 1	sib 2	sib 3	sib4	sib5
Family history stroke (yes=1, no=2, dk=3)							
Family history MI (code other box age)							
Family history PVD (extent)							
Family history brain haemorrhage							
Family history diabetes (treatment)							
Family history hyperlipidaemia							
Family history hypertension							

Adopted Y / N	
Twin Y / N	

Total number of siblings (include interviewee) ☐

Mother	Alive / dead		Age at death	Cause of death
Father	Alive / dead		Age at death	Cause of death
Sibling 1 (Oldest)	Alive / dead	M / F	Age at death	Cause of death
Sibling 2	Alive / dead	M / F	Age at death	Cause of death
Sibling 3	Alive / dead	M / F	Age at death	Cause of death
Sibling 4	Alive / Dead	M / F	Age at death	Cause of death
Sibling 5 (Youngest)	Alive / Dead	M / F	Age at death	Cause of death

Continue on separate page if necessary

Appendix 11 TIA and stroke data collection form (page 11)

Family Tree (number siblings and children)

No of children ☐

History of:	CVA	MI	PVD	ICH	DM	CHOL	HBP
CHILD 1							
CHILD 2							
CHILD 3							
CHILD 4							

Autoimmune History

Y / N / DK	**Personal**	**Family** Number of degree relatives	**Children**
Thyroid			
Early onset diabetes			
Pernicious anaemia			
Rheumatoid arthritis			

Smoking Y / N ☐ lifetime non smoker ☐

Ex-smoker ☐ age ☐ years smoked ☐

Current ☐ no / day ☐ years smoked ☐

Appendix 11 TIA and stroke data collection form (page 12)

Premorbid modified Rankin Y / N

Do you have any symptoms? ☐
Are you able to look after yourself and carry out normal activities? ☐
Does anyone else help pay the bills, do the shopping, cleaning etc? ☐
Do you need someone to help you walk? ☐
Do you need help to wash yourself? ☐
Do you need to be lifted in and out of bed? ☐

0 = no symptoms at all
1 = no significant disability despite symptoms: able to carry out all usual duties and activities
2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3 = moderate disability: requiring some help, but able to walk without assistance
4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6 = death ☐

Rose PVD: IHD questionnaire

Part A

1. Have you ever had any pain or discomfort in your chest? 1=yes 2= no go to part c
2. Do you get the pain or discomfort when you walk up hill or hurry? 1=yes 2=no go to part b
3. Do you get it when you walk at an ordinary pace on the level? 1=yes 2=no
4. When you get any pain or discomfort in your chest what do you do? 1=stop 2=slow down 3=continue at same pace
5. Does it go away when you stand still 1=yes 2=no
6. How soon? 1=10 minutes or less 2= more than 10 minutes

Part B

1. Have you ever had severe pain across the front of your chest lasting half an hour or more? 1=yes 2=no

Part C

1. Do you get pain in either leg when you are walking? 1=yes 2=no (go to next question)
2. Does this pain ever begin when you are standing still or sitting? 1=yes 2=no
3. Do you get this pain in your calf (or calves) 1=yes 2=no
4. Do you get it when you walk up hill or hurry? 1=yes 2=no
5. Do you get it when you walk at an ordinary pace on the level? 1=yes 2=no
6. Does the pain ever disappear while you are still walking? 1=yes 2=no
7. What do you do if you get it when you are walking? 1=stop 2=slow down 3=continue at same pace
8. What happens if you stand still? 1=usually continues for more than 10 minutes 2= usually disappears in 10 minutes or less

Pre-morbid Barthel

	Score
Feeding	
0 = unable	
1 = needs help cutting, spreading butter, etc, or requires modified diet	
2 = independent	
Bathing	
0 = dependent	
1 = independent (or in shower)	
Grooming	
0 = needs help with personal care	
1 = independent face/hair/teeth/shaving (implements provided)	
Dressing	
0 = dependent	
1 = needs help but can do about half unaided	
2 = independent (including buttons, zips, laces, etc.)	
Bowels	
0 = incontinent (or needs to be given enemas)	
1 = occasional accident	
2 = continent	
Bladder	
0 = incontinent, or catheterised and unable to manage alone	
1 = occasional accident	
2 = continent	
Toilet use	
0 = dependent	
1 = needs some help, but can do something alone	
2 = independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	
0 = unable, no sitting balance	
1 = major help (one or two people, physical), can sit	
2 = minor help (verbal or physical)	
3 = independent	
Mobility (on level surfaces)	
0 = immobile	
1 = wheelchair independent, including corners, > 50 metres	
2 = walks with help of one person (verbal or physical) > 50 metres	
3 = independent (but may use any aid; for example, stick) > 50 metres	
Stairs	
0 = unable	
1 = needs help (verbal, physical, carrying aid)	
2 = independent	

Barthel score

Appendix 11 TIA and stroke data collection form (page 14)

ORIENTATION TO TIME		RESPONSE	SCORE	
What is the...	**year?**	_____	0	1
	season?	_____	0	1
	month of the year?	_____	0	1
	day of the week?	_____	0	1
	date?	_____	0	1
				☐

ORIENTATION TO PLACE*

Where are we now? What is the ...

county?	_____	0	1
city/town/village	_____	0	1
street (suburb)	_____	0	1
house name/number (building name)	_____	0	1
room of house (ward number/level)	_____	0	1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted. ☐

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready?

Here they are...APPLE *[pause]*, **PENNY** *[pause]*, **TABLE** *[pause]*. **Now repeat those words back to me.** [Repeat up to 5 times, but score only the first trial.]

APPLE	_____	0	1
PENNY	_____	0	1
TABLE	_____	0	1
			☐

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [Serial 7s]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	{93}	_____	0	1
If needed, say: **Keep going.**	{86}	_____	0	1
If needed, say: **Keep going.**	{79}	_____	0	1
If needed, say: **Keep going.**	{72}	_____	0	1
If needed, say: **Keep going.**	{65}	_____	0	1
		_____		☐

Appendix 11 TIA and stroke data collection form (page 15)

	RESPONSE	SCORE *(circle one)*

Substitute and score this item only if the examinee refuses to perform the Serial 7s task.
Spell the word WORLD forward, then backward, correct forward spelling if misspelled, but score only the backward spelling

(D = 1) (L = 1) (R = 1) (O = 1) (W = 1) (0-5)

RECALL
What were those three words I asked you to remember? *[Do not offer any hints.]*

APPLE _____ 0 1

PENNY _____ 0 1

TABLE _____ 0 1

NAMING*

What is this? [Point to a pencil or pen.] _____ 0 1

What is this? [Point to a watch] _____ 0 1

*Alternative common objects (e.g. eyeglasses, chair, keys may be substituted and noted.

REPETITION
Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that. [Repeat up to 5 times, but score only the first trial.]

NO IFS, ANDS, OR BUTS. _____ 0 1

COMPREHENSION
Listen carefully because I am going to ask you to do something.
Take this paper in your right hand *[pause]*, **fold it in half** *[pause]*, **and put it on the floor (***or* **table).**

TAKE IN RIGHT HAND _____ 0 1

FOLD IN HALF _____ 0 1

PUT ON FLOOR (*or* TABLE) _____ 0 1

READING
Please read this and do what it says. [*Show the examinee the words on the stimulus form*]

CLOSE YOUR EYES _____ 0 1

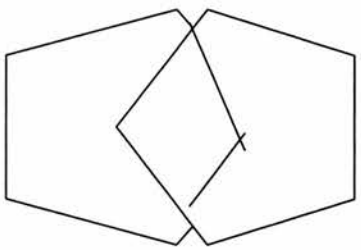
WRITING
Please write a sentence. [*If examinee does not respond, say*: **Write about the weather.**]
Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling. 0 1

DRAWING
Please copy this design. [*Display the intersecting pentagons on the stimulus form.*]
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure. 0 1

TOTAL SCORE (maximum 30)

Appendix 11 TIA and stroke data collection form (page 16)

CLOSE YOUR EYES



Any reason why MMSE is not optimal in this patient?

Onset anger scale

Anger level	Description
1	**Calm**
2	**Busy** (but not hassled)
3	**Mildly angry** (irritated, and hassled, but does not show)
4	**Moderately angry** (so hassled it shows in your voice)
5	**Very angry** (body tense, clenching fists or teeth)
6	**Furious** (almost out of control, very angry, pound table)
7	**Enraged** (lost control, throwing objects, hurting yourself or

In the two hours prior to the event what best describes your emotional state from the above list (1 – 7)? ☐

In the exact same two hours on the day prior to your event which best describes your mood (1 – 7)? ☐

If you had your event on wakening how were you in the two hours before you went to bed (1 – 7)? ☐

Interviewer's perception of patient personality (see scale below)? ☐

Appendix 11 TIA and stroke data collection form (page 17)

In general with regard to stress what kind of person do you think you are? 1=Very relaxed, 2=Fairly relaxed, 3=Average, 4=Prone to stress, 5=Highly stressed

Place of residence: 1=Home, 2=home of relative, 3=home of friend, 4=warden housing, 5=care home, 9=other(specify)

Do you live alone? Y / N

If no with whom

Are you a carer? Y / N
Physical help to wash / dress / transfer or walk

Does anyone assist you at home?
1=Spouse, 2=relative, 3=private carer, 4=community services (specify)

Marital status
married=1, widow=2, single=3, separated=4, partner=5, 9=not k

Contacts with close friends and relatives
How many times do you see a friend or relative each week?
0 – 1 2 – 3 4 – 7 >7

Employment status
Working f/t=1, p/t=2, caring for home=3, unemployed=4, unable to work=5, retired=6, student=7

Most recent occupation
(husband occupation if not employed)

Socioeconomic class (I – VI)

Ethnic origin
1=white, 2=black caribbean, 3=black african, 4=indian, 5=pakistani, 6=bangladeshi, 7=chinese, 8=other

Exercise
Clinician judgement on amount of physical activity (age corrected) per week. 1=None, 2=Below average, 3=Normal, 4=Above average

Alcohol units per week

Education Age left school

1= Basic, 2=Further, 3=Higher

Age left full time education

Appendix 11 TIA and stroke data collection form (page 18)

Sleep

What is the likelihood of you dozing in the following situation?

0 = no chance of dozing, 1 = slight chance of dozing,
2 = moderate chance of dozing,3= high chance of dozing

Sitting and reading	0	1	2	3	☐
Lying down to rest in the afternoon when circumstances permit	0	1	2	3	☐
Sitting and talking to someone	0	1	2	3	☐

On average how many hours sleep do you get per night? ☐

Do you snore? Y / N ☐

Have you been told by someone that you stop breathing at night? ☐

Do you take medications for high blood pressure? Y / N ☐

People tell me that I snore
(Use scale below:score 1 – 8) ☐

I have been told by other people that I gasp, choke or snort while I am sleeping ☐
(Use scale below:score 1 – 8)
1=Never, 2=Rarely (1-2X / year), 3=Occasionally (4-8X / year), 4=sometimes (1-2X / month), 5=Often (1-2X / week), 6=Usually (3-5X / week), 7=Always (every night), 8=I don't know

Nutrition

How is your appetite? Good normal poor uncertain ☐

Do you think you have a healthy diet? Y / N / DK ☐

On average how many portions of fish do you eat per week? ☐
1=Less than once per week, 2=once per week, 3=twice a week, 3=>=three times per week

Do you add salt to your food? Y / N ☐

Do you drink full fat (1) or low fat (2) milk ☐

On average how many portions of fresh fruit and vegetables do you eat? 1=Less than once per week, 2=one portion per week, 3=several portions per week, 4=once per day, 5=2-4 portions per day, 6=>=5 portions per day ☐

Appendix 11 TIA and stroke data collection form (page 19)

Mood
Do you often feel sad or depressed? Y / N

Driving
Do you drive? Y / N

Handedness
R=Right / L=left / B=both / DK=not known

Clinician impression of frailty (corrected for age)

1=Frail 2=Normal

Life events
Has any of the following unpleasant things happened to you over the last year?
For each answer yes or no Y=1 N=2
Then ask how upset were you by these events?
Very much (1) / moderately (2) / not too much (3)

Death or serious illness of close friend or relative?

Financial difficulty

Divorce or break up of close friends or relatives

Major conflict with children or grandchildren

Muggings / robberies / accidents

Other (specify)

For women

Age of first pregnancy

Number of pregnancies

Age of last pregnancy

Age of menopause

Miscarriage Y / N

Number

OCP Y / N

HRT Y / N

No. of years on HRT/OCP

Appendix 11 TIA and stroke data collection form (page 20)

General Examination

Collar size (cm)

Waist measurement (cm)

Hip measurement (cm)

Waist / hip ratio

Weight (kg)

Height (m)

BMI

Arcus Y / N

Xanthelasma Y / N

Ear crease Y / N

Nicotine staining Y / N

Own teeth / denture

Temperature on admission (if inpatient)

Pulse on admission
1=Bradycardia (<60) 2=Normal (60 –99) 3=Tachycardia >=100

1=sinus rhythm 2=AF 3=Other

Blood pressure on admissio Sats / air% BM

Pulse at assessment

Blood pressure at assessment

Bruits	Right	Left
Carotid		
Renal		
Femoral		
Subclavian		
Vertebral		

Cardiac murmur Y / N CCF Y /N

Any pre-existing neurological disability? Y / N

Appendix 11 TIA and stroke data collection form (page 21)

Stroke
Prestroke disability (Rankin <3) ☐ Predicted 30 day Rankin ☐

Symptoms at onset Y / N /DK Date Time
Findings on examination

Weakness			sensory			visual			other		
	Right	left		right	left		right	left		yes	no
Face			face			hemianopia			dysphasia		
Arm			arm			monocular			dysarthria		
Hand			hand				yes	no	vertigo		
Leg			leg			diplopia			headache		

Findings on examination

GCS Eyes / 4 Motor / 6 Verbal / 5 ☐

Weakness			sensory		eyes / vision		other	other	
	Right	left	right	left	yes	no	yes	no	
Face		face			heminopia		dysphasia		
Arm		arm			gazepalsy		dysarthria		
Hand		hand			nystagmus		ataxia		
leg		leg					neglect		

NIH stroke scale

LOC	☐	LOC questions	☐	LOC commands	☐
Best gaze	☐	Best visual	☐	Facial Pasy	☐
Right Arm	☐	Left Arm	☐	Right Leg	☐
Left Leg	☐	Limb Ataxia	☐	Sensory	☐
Language	☐	Dysarthria	☐	Neglect	☐

Total ☐

Appendix 11 TIA and stroke data collection form (page 22)

Prognosis

Date of following prognostic markers

no deficit=1 / mild = 2 / mod =3 / severe = 4

Hemianopia

Inattention

Dysarthria

Swallowing

Dysphasia

Limb deficit Y / N
Able to lift both harms to horizontal MRC>=3

Unable to sit independently Y / N

Unable to stand independently Y/N

Unable to walk independently Y / N
Walks without help of another – can use aid

Urinary incontinence Y / N

Catheterised Y / N

Appendix 11 TIA and stroke data collection form (page 23)

Management

Y / N

Diet

Weight reduction

Smoking

Drug management	New	Continued
Aspirin		
Dipyridamole		
Clopidogrel		
Warfarin		
Lipid lowering		
Antihypertensive		
ACE Inhibitors		
Thiazide diuretics		
Loop diuretics		
Betablockers		
Antiarrythmics		
Angioplasty		
Stent		
Surgery		

Appendix 11 TIA and stroke data collection form (page 24)

Discharge

Length of stay in acute hospital

Length of stay rehab hospital

Total length of stay

Readmission before 30 days

Number of readmissions

30 day case fatality 1=alive 2=dead

Clinical diagnosis at discharge
Copy immediate discharge letter

Appendix 12 STEMI data collection form (page 1)

ID NO:

Patient identification label

Telephone

Next of kin / contact / relationship

Address

Telephone NOK

Consultant

Examiner

GP Details

Beaumont street	01	East Oxford	03	Berinsfield	04
Malthouse	05	Kidlington	06	Wantage	07
Marcham Rd	08	Stert street	09	Other	10

Summary diagnosis

ST elevation Y / N

ST elevation – Lytic Y / N

ST elevation – No Lytic

Troponin >0.2 Y / N

CK rise (>2X) Y / N

New Q waves Y / N

New LBBB

Is this the first ever in lifetime (incident) ACS? Y / N

Date of notification event

Event leading to notification

Location of interview:

1=JRH in patient / 2=RI in patient / 3=community hospital / 4=outpatients / 5=home / 6=other (specify)

Follow-up plan at 1 month

1=RI TIA clinic / 2=ACS-Primary Care / 3=Refused follow-up / 4=other/ 5=CVA-Primary Care

Information on form obtained from 1=patient / 2=relative / 3=GP / 4=hospital records / 5=death certificate / 6=other

Source of first notification GP=1 / JRH admissions=2 / other hospital=3 / other referrals=4 / health authority search=5 / death=6 / troponin=7/other=9

Other sources of notification(include 1st 2. 3. 4.

Please specify

If one had not identified the patient via the route of first notification would patient been identified by other source of ascertainment? Y / N

Appendix 12 STEMI data collection form (page 2)

Narrative history & examination

Symptoms Chest pain Y / N ☐ Radiation to arms or neck Y/ N ☐

SOB Y/N ☐ Description ☐

Duration of chest pain in minutes ☐

Notification event date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
(The event that led to GP notification)

What did you think was wrong?

☐

Were you alone? Y / N ☐

If you were with someone who was it? ☐

Who called for help? ☐

If you did not call for help at time of event, why not?

☐

Who did you (or person with you) first call for help? 1=medical / 2=non medical ☐

First call for help date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
(if medical code '9s')

First call to GP / A&E date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
/ 999 i.e medical

Outcome of first call for medical assistance

☐

Seen by GP / A&E date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐

GP notification to date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
OXVASC/ascertainment

Admission (if admitted) date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐

Assessment date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐

Appendix 12 STEMI data collection form (page 3)

If onset on wakening from sleep Y / N ☐ time awake ☐

Activity at onset (within two hour of onset)
Estimated no. of met: asleep (1 met); sedentary (2 met); mild-mod activity (3-5 met); strenuous (>6 met) *(need list)* ☐

What were you doing in the same 2 hours on the day prior to the event? Estimated no. of met: asleep (1 met); sedentary (2 met); mild-mod activity (3-5 met); strenuous (>6 met) *(need list)* ☐

Exact circumstances at time of onset of event Y / N

Standing ☐ Sitting ☐ Lying down ☐

Drugs within previous1 hour ☐ Meal within previous one hour ☐

Record exact activity ☐

Location of event ☐

If admitted (use yellow ambulance sheet)

Arrival of emergency service date ☐ time ☐

Arrival in hospital date ☐ time ☐
(If not on ambulance sheet use blue admissions)

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	NSTEMI or STEMI	Cerebral TIA CVA	Peripheral
Number of events			
Date of most recent			

Appendix 12 STEMI data collection form (page 4)

Delay from onset of symptoms to call for help

Delay from call for help to arrival ambulance / GP OPD

Delay from call for help to arrival hospital / GP

Background Medical History

Angina Y / N Age at diagnosis

Hypertension Y / N Age at diagnosis

Myocardial infarction Y / N Age at diagnosis

Diabetes mellitus Y / N Age at diagnosis

Treatment: Diet Tablets Y / N

Insulin Y / N

Valvular heart disease Y / N Age at diagnosis

Nature:

Intermittent claudication Y / N Age at diagnosis

Peripheral vascular intervention

Y / N Age at first intervention

Site:

Type: angiogram angioplasty bypass amputation

Result

Atrial fibrillation Y / N Age at diagnosis

1=Current / 2=Previous

1=Cardioversion, 2=paroxysmal, 3=persistent, 4=permanent

Pacemaker Y / N Type

Hyperlipidaemia Y / N / DK Age at diagnosis

Treatment: Diet Y / N Statin Y / N Other

Appendix 12 STEMI data collection form (page 5)

Cardiac failure Y / N ☐ Age at diagnosis ☐ Treated ☐

Migraine Y / N ☐ With aura Y / N ☐

Prolonged aura (>1h) Y / N ☐

Epilepsy Y / N ☐ Age at diagnosis ☐

Cardiac intervention Y / N ☐ age at first interventic ☐

Angiogram ☐ angioplasty ☐ stent ☐ bypass ☐

Result angiogram
LM / LAD / LCx / RCA
Mild < 50%
Moderate 51–59%
Severe >60%
Bypass grafts ☐

Carotid endarterectomy Y / N ☐ Age at operation ☐ Side ☐

Asthma Y / N ☐
COAD Y / N ☐

Liver disease Y / N ☐
Peptic ulcer disease ☐

Any previous venous thromboses Y / N ☐ No. ☐
Give details below

☐

Any other past medical history

☐

Appendix 12 STEMI data collection form (page 6)

SLE (look in notes) Y / N ☐ Age of diagnosis ☐

Anticardiolipin antibodies (aCL) Y/ N / DK ☐

Lupus anticoagulant (LA) Y / N / DK ☐

Autoimmune disease Y / N ☐
If so give diagnosis:

☐

Allergies ☐

Nosebleeds Y / N ☐ **Bleeding after dental extraction** Y / N ☐

Any cancer ☐ **End stage renal failure / dialysis** ☐

List of medications <u>before onset</u> of notification event

Aspirin Y / N ☐ Dose ☐

Dipyridamole Y / N ☐

Clopidogrel Y / N ☐

Warfarin Y / N ☐ INR ☐

Aspirin Resistance (ask re drugs in 10 days prior to assessment)

Were you on aspirin before this event? Y/N ☐ Date started? ☐

Have you had aspirin since this acute event? Y/N ☐

What doses? (date & dose) ☐

Were you on clopidogrel before this event? Y / N ☐ Date started? ☐

Have you had clopidogrel since this acute event? Y / N ☐

What doses? (date & dose) ☐

Have you had any anti inflammatories in 10 days prior to assessment? Y / N ☐

What drug and doses? ☐

Appendix 12 STEMI data collection form (page 7)

Do you take vitamin supplements? Y / N

B6 Y / N FOLATE Y / N B12 Y / N

List names of supplements

Other medication : *scroll of other drugs on database*

Was your BP measured at any time prior to the notification event?

Date of most recent BP measurement prior to notification event

How many times have you had your BP measured in the last year?

Over the last 10 years how many times have you had your BP measured? 1=none, 2=one to two times, 3=three to five times, 4=more than five times, 9=don't know

Previous stroke or TIA Since 1/4/02		date recent	previous yes	previous no	no of events	date 1st event	duration recent	duration longest
Hemispheric stroke carotid	right						xxx	xxxxx
	left						xxx	xxxxx
Hemisheric TIA carotid	right							
	left							
Vertebrobasilar stroke							xxx	xxxxx
Vertebrobasilar TIA								
Stroke unknown territory							xxx	xxxxx
TIA unknown territory								
Amaurosis fugax	right							
	left							
Retinal infarction	right						xxx	xxxxx
	Left						xxx	xxxx

Appendix 12 STEMI data collection form (page 8)

FAMILY HISTORY	dad	mum	sib 1	sib 2	sib 3	sib4	sib5
Family history stroke (yes=1, no=2, dk=3)							
Family history MI (code other box age)							
Family history PVD (extent)							
Family history brain haemorrhage							
Family history diabetes (treatment)							
Family history hyperlipidaemia							
Family history hypertension							

Adopted Y / N	
Twin Y / N	

Total number of siblings (include interviewee) ☐

Mother	Alive / dead		Age at death	Cause of death
Father	Alive / dead		Age at death	Cause of death
Sibling 1 (Oldest)	Alive / dead	M / F	Age at death	Cause of death
Sibling 2	Alive / dead	M / F	Age at death	Cause of death
Sibling 3	Alive / dead	M / F	Age at death	Cause of death
Sibling 4	Alive / Dead	M / F	Age at death	Cause of death
Sibling 5 (Youngest)	Alive / Dead	M / F	Age at death	Cause of death

Continue on separate page if necessary

Appendix 12 STEMI data collection form (page 9)

Family Tree (number siblings and children)

No of children ☐

History of:	CVA	MI	PVD	ICH	DM	CHOL	HBP
CHILD 1							
CHILD 2							
CHILD 3							
CHILD 4							

Autoimmune History

Y / N / DK	**Personal**	**Family** Number of degree relatives	**Children**
Thyroid			
Early onset diabetes			
Pernicious anaemia			
Rheumatoid arthritis			

Smoking Y / N ☐ lifetime non smoker ☐

Ex-smoker ☐ age ☐ years smoked ☐

Current ☐ no / day ☐ years smoke ☐

Appendix 12 STEMI data collection form (page 10)

Premorbid modified Rankin Y / N

Do you have any symptoms? ☐
Are you able to look after yourself and carry out normal activities? ☐
Does anyone else help pay the bills, do the shopping, cleaning etc? ☐
Do you need someone to help you walk? ☐
Do you need help to wash yourself? ☐
Do you need to be lifted in and out of bed? ☐

0 = no symptoms at all
1 = no significant disability despite symptoms: able to carry out all usual duties and activities
2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3 = moderate disability: requiring some help, but able to walk without assistance
4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6 = death ☐

Rose PVD: IHD questionnaire

Part A

1. Have you ever had any pain or discomfort in your chest? 1=yes 2= no go to part c
2. Do you get the pain or discomfort when you walk up hill or hurry? 1=yes 2=no go to part b
3. Do you get it when you walk at an ordinary pace on the level? 1=yes 2=no
4. When you get any pain or discomfort in your chest what do you do? 1=stop 2=slow down 3=continue at same pace
5. Does it go away when you stand still 1=yes 2=no
6. How soon? 1=10 minutes or less 2= more than 10 minutes

Part B

1. Have you ever had severe pain across the front of your chest lasting half an hour or more? 1=yes 2=no

Part C

1. Do you get pain in either leg when you are walking? 1=yes 2=no (go to next question)
2. Does this pain ever begin when you are standing still or sitting? 1=yes 2=no
3. Do you get this pain in your calf (or calves) 1=yes 2=no
4. Do you get it when you walk up hill or hurry? 1=yes 2=no
5. Do you get it when you walk at an ordinary pace on the level? 1=yes 2=no
6. Does the pain ever disappear while you are still walking? 1=yes 2=no
7. What do you do if you get it when you are walking? 1=stop 2=slow down 3=continue at same pace
8. What happens if you stand still? 1=usually continues for more than 10 minutes 2= usually disappears in 10 minutes or less

Appendix 12 STEMI data collection form (page 11)

Pre-morbid Barthel

	Score
Feeding	
0 = unable	
1 = needs help cutting, spreading butter, etc, or requires modified diet	
2 = independent	
Bathing	
0 = dependent	
1 = independent (or in shower)	
Grooming	
0 = needs help with personal care	
1 = independent face/hair/teeth/shaving (implements provided)	
Dressing	
0 = dependent	
1 = needs help but can do about half unaided	
2 = independent (including buttons, zips, laces, etc.)	
Bowels	
0 = incontinent (or needs to be given enemas)	
1 = occasional accident	
2 = continent	
Bladder	
0 = incontinent, or catheterised and unable to manage alone	
1 = occasional accident	
2 = continent	
Toilet use	
0 = dependent	
1 = needs some help, but can do something alone	
2 = independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	
0 = unable, no sitting balance	
1 = major help (one or two people, physical), can sit	
2 = minor help (verbal or physical)	
3 = independent	
Mobility (on level surfaces)	
0 = immobile	
1 = wheelchair independent, including corners, > 50 metres	
2 = walks with help of one person (verbal or physical) > 50 metres	
3 = independent (but may use any aid; for example, stick) > 50 metres	
Stairs	
0 = unable	
1 = needs help (verbal, physical, carrying aid)	
2 = independent	

Barthel score

Appendix 12 STEMI data collection form (page 12)

ORIENTATION TO TIME		RESPONSE	SCORE
What is the...	**year?**	_____	0 1
	season?	_____	0 1
	month of the year?	_____	0 1
	day of the week?	_____	0 1
	date?	_____	0 1
			[ ]

ORIENTATION TO PLACE*

Where are we now? What is the ...

county?	_____	0 1
city/town/village	_____	0 1
street (suburb)	_____	0 1
house name/number (building name)	_____	0 1
room of house (ward number/level)	_____	0 1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted. [ ]

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready?

Here they are...APPLE *[pause]*, **PENNY** *[pause]*, **TABLE** *[pause]*. **Now repeat those words back to me.** [Repeat up to 5 times, but score only the first trial.]

APPLE	_____	0 1
PENNY	_____	0 1
TABLE	_____	0 1
		[ ]

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [Serial 7s]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	{93}	_____	0 1
If needed, say: **Keep going.**	{86}	_____	0 1
If needed, say: **Keep going.**	{79}	_____	0 1
If needed, say: **Keep going.**	{72}	_____	0 1
If needed, say: **Keep going.**	{65}	_____	0 1
		_____	[ ]

Appendix 12 STEMI data collection form (page 13)

RESPONSE — SCORE *(circle one)*

Substitute and score this item only if the examinee refuses to perform the Serial 7s task.
Spell the word WORLD forward, then backward, correct forward spelling if misspelled, but score only the backward spelling

(D = 1) (L = 1) (R = 1) (O = 1) (W = 1) (0-5)

RECALL
What were those three words I asked you to remember? *[Do not offer any hints.]*

APPLE _____ 0 1

PENNY _____ 0 1

TABLE _____ 0 1

NAMING*

What is this? [Point to a pencil or pen.] _____ 0 1

What is this? [Point to a watch] _____ 0 1

*Alternative common objects (e.g. eyeglasses, chair, keys may be substituted and noted.

REPETITION
Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that. [Repeat up to 5 times, but score only the first trial.]

NO IFS, ANDS, OR BUTS. _____ 0 1

COMPREHENSION
Listen carefully because I am going to ask you to do something.
Take this paper in your right hand *[pause]*, **fold it in half** *[pause]*, **and put it on the floor (***or* **table).**

TAKE IN RIGHT HAND _____ 0 1

FOLD IN HALF _____ 0 1

PUT ON FLOOR (*or* TABLE) _____ 0 1

READING
Please read this and do what it says. [*Show the examinee the words on the stimulus form*]

CLOSE YOUR EYES _____ 0 1

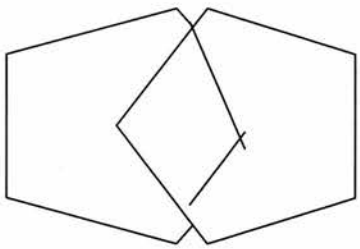
WRITING
Please write a sentence. [*If examinee does not respond, say*: **Write about the weather.**]
Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling. 0 1

DRAWING
Please copy this design. [*Display the intersecting pentagons on the stimulus form.*] 0 1
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

TOTAL SCORE (maximum 30)

Appendix 12 STEMI data collection form (page 14)

CLOSE YOUR EYES



Any reason why MMSE is not optimal in this patient?

Onset anger scale

Anger level	Description
1.	**Calm**
2.	**Busy** (but not hassled)
3.	**Mildly angry** (irritated, and hassled, but does not show)
4.	**Moderately angry** (so hassled it shows in your voice)
5.	**Very angry** (body tense, clenching fists or teeth)
6.	**Furious** (almost out of control, very angry, pound table)
7.	**Enraged** (lost control, throwing objects, hurting yourself

In the two hours prior to the event what best describes your emotional state from the above list (1 – 7)? ☐

In the exact same two hours on the day prior to your event which best describes your mood (1 – 7)? ☐

If you had your event on wakening how were you in the two hours before you went to bed (1 – 7)? ☐

Interviewer's perception of patient personality (see scale below)? ☐

Appendix 12 STEMI data collection form (page 15)

In general with regard to stress what kind of person do you think you are? 1=Very relaxed, 2=Fairly relaxed, 3=Average, 4=Prone to stress, 5=Highly stressed

Place of residence: 1=Home, 2=home of relative, 3=home of friend, 4=warden housing, 5=care home, 9=other(specify)

Do you live alone? Y / N

If no with whom

Are you a carer? Y / N
Physical help to wash / dress / transfer or walk

Does anyone assist you at home?
1=Spouse, 2=relative, 3=private carer, 4=community services (specify)

Marital status
married=1, widow=2, single=3, separated=4, partner=5, 9=not k

Contacts with close friends and relatives
How many times do you see a friend or relative each week?
0 – 1 2 – 3 4 – 7 >7

Employment status
Working f/t=1, p/t=2, caring for home=3, unemployed=4, unable to work=5, retired=6, student=7

Most recent occupation
(husband occupation if not employed)

Socioeconomic class (I – VI)

Ethnic origin
1=white, 2=black caribbean, 3=black african, 4=indian, 5=pakistani, 6=bangladeshi, 7=chinese, 8=other

Exercise
Clinician judgement on amount of physical activity (age corrected) per week. 1=None, 2=Below average, 3=Normal, 4=Above average

Alcohol units per week

Education Age left school

1= Basic, 2=Further, 3=Higher

Age left full time education

Appendix 12 STEMI data collection form (page 16)

Sleep

What is the likelihood of you dozing in the following situation?

0 = no chance of dozing, 1 = slight chance of dozing,
2 = moderate chance of dozing,3= high chance of dozing

Sitting and reading	0	1	2	3	☐
Lying down to rest in the afternoon when circumstances permit	0	1	2	3	☐
Sitting and talking to someone	0	1	2	3	☐

On average how many hours sleep do you get per night? ☐

Do you snore? Y / N ☐

Have you been told by someone that you stop breathing at night? ☐

Do you take medications for high blood pressure? Y / N ☐

People tell me that I snore
(Use scale below:score 1 – 8) ☐

I have been told by other people that I gasp, choke or snort while I am sleeping
(Use scale below:score 1 – 8) ☐

1=Never, 2=Rarely (1-2X / year), 3=Occasionally (4-8X / year), 4=sometimes (1-2X / month), 5=Often (1-2X / week), 6=Usually (3-5X / week), 7=Always (every night), 8=I don't know

Nutrition

How is your appetite? Good normal poor uncertain ☐

Do you think you have a healthy diet? Y / N / DK ☐

On average how many portions of fish do you eat per week?
1=Less than once per week, 2=once per week, 3=twice a week, 3=>=three times per week ☐

Do you add salt to your food? Y / N ☐

Do you drink full fat (1) or low fat (2) milk ☐

On average how many portions of fresh fruit and vegetables do you eat? 1=Less than once per week, 2=one portion per week, 3=several portions per week, 4=once per day, 5=2-4 portions per day, 6=>=5 portions per day ☐

Appendix 12 STEMI data collection form (page 17)

Mood
Do you often feel sad or depressed? Y / N

Driving
Do you drive? Y / N

Handedness
R=Right / L=left / B=both / DK=not known

Clinician impression of frailty (corrected for age)

1=Frail 2=Normal

Life events
Has any of the following unpleasant things happened to you over the last year?
For each answer yes or no Y=1 N=2
Then ask how upset were you by these events?
Very much (1) / moderately (2) / not too much (3)

Death or serious illness of close friend or relative?

Financial difficulty

Divorce or break up of close friends or relatives

Major conflict with children or grandchildren

Muggings / robberies / accidents

Other (specify)

For women

Age of first pregnancy

Number of pregnancies

Age of last pregnancy

Age of menopause

Miscarriage Y / N

Number

OCP Y / N

HRT Y / N

No. of years on HRT/OCP

Appendix 12 STEMI data collection form (page 18)

General Examination

Collar size (cm)

Waist measurement (cm)

Hip measurement (cm)

Waist / hip ratio

Weight (kg)

Height (m)

BMI

Arcus Y / N

Xanthelasma Y / N

Ear crease Y / N

Nicotine staining Y / N

Own teeth / denture

Temperature on admission (if inpatient)

Pulse on admission
1=Bradycardia (<60) 2=Normal (60 –99) 3=Tachycardia >=100

1=sinus rhythm 2=AF 3=Other

Blood pressure on admissio Sats / air% BM

Pulse at assessment

Blood pressure at assessment

Bruits	Right	Left
Carotid		
Renal		
Femoral		
Subclavian		
Vertebral		

Cardiac murmur Y / N CCF Y /N

Any pre-existing neurological disability? Y / N

Appendix 12 STEMI data collection form (page 19)

Myocardial Infarction

Time and date of reperfusion treatment
(No thrombolysis=9)

Delay from arrival in hospital to reperfusion treatment

Time and date first cardiac arrest
(no cardiac arrest=9)

Territory 1=Anterior, 2=LBBB, 3=Inferior, 4=other

Cardiac arrest
1=no arrest, 2=before ambulance, 3=after ambulance,
4=A&E, 5=CCU, 6=medical ward, 7=elsewhere in hospita

Presenting rhythm
1=no arrest, 2=asystole, 3=VF/pulseless VT,
4=EMD 9=N/A or DK

Outcome
1=no return circulation
2=return spontaneous circulation died in hospital
3=discharged from hospital with neuro deficit
4=discharged no neuro deficit
5=resuscitation not attempted
6=no arrest
9=not known / not applicable

Admission diagnosis
1=definite MI, 2=probable MI, 3=unstable angina,
4=chest pain, 5=other initial diagnosis
6=already in hospital

ECG determining treatment
1=ST elevation, 2=LBBB, 3=ST depression,
4=T wave change, 5=other, 6=normal,
9=not known

Appendix 12 STEMI data collection form (page 20)

Reperfusion attempted
1=thrombolysis, 2=ptca, 3=rescue ptca, 5=not attempted
9=not known

Did patient receive aspirin
1=already on, 2=given out of hospital, 3=after arrival,
4=ci to aspirin, 5=other antiplatelet, 6=none,
7=on warfarin, 8=not known

Admission unit
1=ccu, 2=AMAU, 3=gen med ward, 4=ITU, 5=other,
6=died A&E, 7=cardiac ward, 8=stepdown

Killip 1=I 2=II / III / IV

Diuretic initiated or increased for heart failure?
1=yes 2=no 9=unknown

Cardiac enzymes

	CK	peak	AST	LDH	troponin	peak
Dates Admission						
Day 1						
Day 2						
Day 3						

Intervention at this admission

Angiogram

Angioplasty

Stent

CABG

TIMI – STEMI score

Age (>=75 = 3 / 65-74 = 2)

DM or HBP or angina = 1

SBP<100 = 3

HR>100 = 2

Killip II – IV = 2

Weight<67kg = 1

Anterior STE / LBBB =1

Time to Tx > 4 = 1

Appendix 12 STEMI data collection form (page 21)

Management

Y / N

Diet

Weight reduction

Smoking

Drug management	New	Continued
Aspirin		
Dipyridamole		
Clopidogrel		
Warfarin		
Lipid lowering		
Antihypertensive		
ACE Inhibitors		
Thiazide diuretics		
Loop diuretics		
Betablockers		
Antiarrythmics		
LMWH		

Other

Procedures Pacing IABP Echo

Swan-Ganz

Angiogram Angioplasty

Stent Bypass /repair

Appendix 12 STEMI data collection form (page 22)

Discharge

Length of stay in acute hospital

Length of stay rehab hospital

Total length of stay

Readmission before 30 days

Number of readmissions

30 day case fatality 1=alive 2=dead

Clinical diagnosis at discharge
Copy immediate discharge letter

Appendix 13 Acute peripheral vascular event data collection form (page 1)

ID NO:
Patient identification label

Telephone

Next of kin / contact / relationship
Address

Telephone NOK

Consultant

Examiner

GP Details

Beaumont street	01	East Oxford	03	Berinsfield	04
Malthouse	05	Kidlington	06	Wantage	07
Marcham Rd	08	Stert street	09	Other	10

Summary diagnosis

Embolism Site

Acute on chronic thrombosis Site

Aneurysm Site
Rupture Leak

Is this the first ever (incident PVD) event? Y / N

Date of notification event
Event leading to notification
Location of interview:
1=JRH in patient / 2=RI in patient / 3=community hospital / 4=outpatients / 5=home / 6=other (specify)

Follow-up plan at 1 month
1=RI TIA clinic / 2=ACS-Primary Care / 3=Refused follow-up / 4=other/ 5=CVA-Primary Care

Information on form obtained from 1=patient / 2=relative / 3=GP / 4=hospital records / 5=death certificate / 6=other

Source of first notification GP=1 / JRH admissions=2 / other hospital=3 / other referrals=4 / health authority search=5 / death=6 / troponin=7/other=9

Other sources of notification(include 1st 2. 3. 4.
Please specify
If one had not identified the patient via the route of first notification would patient been identified by other source of ascertainment? Y / N

Appendix 13 Acute peripheral vascular event data collection form (page 2)

Narrative history & examination

Notification event date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
(The event that led to GP notification)

What did you think was wrong?

Were you alone? Y / N ☐

If you were with someone who was it? ☐

Who called for help? ☐

If you did not call for help at time of event, why not?

Who did you (or person with you) first call for help? 1=medical / 2=non medical ☐

First call for help date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
(if medical code '9s')

First call to GP / A&E date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
/ 999 i.e medical

Outcome of first call for medical assistance

Seen by GP / A&E date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐

GP notification to date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐
OXVASC/ascertainment

Admission (if admitted) date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐

Assessment date ☐☐ ☐☐ ☐☐ time ☐☐ ☐☐

Appendix 13 Acute peripheral vascular event data collection form (pg 3)

If onset on wakening from sleep Y / N ☐ time awake ☐

Activity at onset (within two hour of onset)
Estimated no. of met: asleep (1 met); sedentary (2 met); mild-mod ☐ 5 met); strenuous (>6 met) *(need list)*

What were you doing in the same 2 hours on the day prior to the event? Estimated no. of met: asleep (1 met); sedentary (2 met); mild-mod activity (3-5 met); stre ☐ et) *(need list)*

Exact circumstances at time of onset of event Y / N

Standing ☐ Sitting ☐ Lying down ☐

Drugs within previous1 hour ☐ Meal within previous one hour ☐

Record exact activity ☐

Location of event ☐

If admitted (use yellow ambulance sheet)

Arrival of emergency service date ☐ time ☐

Arrival in hospital date ☐ time ☐
(If not on ambulance sheet use blue admissions)

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	NSTEMI or STEMI	Cerebral TIA CVA	Peripheral
Number of events			
Date of most recent			

Appendix 13 Acute peripheral vascular event data collection form (pg 4)

Delay from onset of symptoms to call for help

Delay from call for help to arrival ambulance / GP OPD

Delay from call for help to arrival hospital / GP

Background Medical History

Angina Y / N Age at diagnosis

Hypertension Y / N Age at diagnosis

Myocardial infarction Y / N Age at diagnosis

Diabetes mellitus Y / N Age at diagnosis

Treatment: Diet Tablets Y / N

Insulin Y / N

Valvular heart disease Y / N Age at diagnosis

Nature:

Intermittent claudication Y / N Age at diagnosis

Peripheral vascular intervention

Y / N Age at first intervention

Site:

Type: angiogram angioplasty bypass amputation

Result

Atrial fibrillation Y / N Age at diagnosis

1=Current / 2=Previous

1=Cardioversion, 2=paroxsymal, 3=persistent, 4=permanent

Pacemaker Y / N Type

Hyperlipidaemia Y / N / DK Age at diagnosis

Treatment: Diet Y / N Statin Y / N Other

Appendix 13 Acute peripheral vascular event data collection form (pg 5)

Cardiac failure Y / N ☐ Age at diagnosis ☐ Treated ☐

Migraine Y / N ☐ With aura Y / N ☐

Prolonged aura (>1h) Y / N ☐

Epilepsy Y / N ☐ Age at diagnosis ☐

Cardiac intervention Y / N ☐ age at first intervention ☐

Angiogram ☐ angioplasty ☐ stent ☐ bypass ☐

Result angiogram
LM / LAD / LCx / RCA
Mild < 50%
Moderate 51–59%
Severe >60%
Bypass grafts ☐

Carotid endarterectomy Y / N ☐ Age at operation ☐ Side ☐

Asthma Y / N ☐
COAD Y / N ☐

Liver disease Y / N ☐
Peptic ulcer disease ☐

Any previous venous thromboses Y / N ☐ No. ☐
Give details below

☐

Any other past medical history ☐

SLE (look in notes) Y / N ☐ Age of diagnosis ☐

Anticardiolipin antibodies (aCL) Y / N / DK ☐

Lupus anticoagulant (LA) Y / N / DK ☐

Appendix 13 Acute peripheral vascular event data collection form (pg 6)

Autoimmune disease Y / N
If so give diagnosis:

Allergies

Nosebleeds Y / N

Bleeding after dental extraction Y / N

Any cancer

End stage renal failure / dialysis

List of medications <u>before onset</u> of notification event

Aspirin Y / N Dose

Dipyridamole Y / N

Clopidogrel Y / N

Warfarin Y / N INR

Aspirin Resistance (ask re drugs in 10 days prior to assessment)

Were you on aspirin before this event? Y/N Date started?

Have you had aspirin since this acute event? Y/N

What doses? (date & dose)

Were you on clopidogrel before this event? Y / N Date started?

Have you had clopidogrel since this acute event?Y / N

What doses? (date & dose)

Have you had any anti inflammatories in 10 days prior to assessment? Y / N

What drug and doses?

Do you take vitamin supplements? Y / N

B6 Y / N FOLATE Y / N B12 Y / N

Appendix 13 Acute peripheral vascular event data collection form (pg 7)

List names of supplements

Other medication : *scroll of other drugs on database*

Was your BP measured at any time prior to the notification event?

Date of most recent BP measurement prior to notification event

How many times have you had your BP measured in the last year?

Over the last 10 years how many times have you had your BP measured? 1=none, 2=one to two times, 3=three to five times, 4=more than five times, 9=don't know

Previous stroke or TIA Since 1/4/02		date recent	previous yes	previous no	no of events	date 1st event	duration recent	duration longest
Hemispheric stroke carotid	right						xxx	xxxxx
	left						xxx	xxxxx
Hemisheric TIA carotid	right							
	left							
Vertebrobasilar stroke							xxx	xxxxx
Vertebrobasilar TIA								
Stroke unknown territory							xxx	xxxxx
TIA unknown territory								
Amaurosis fugax	right							
	left							
Retinal infarction	right						xxx	xxxxx
	Left						xxx	xxxx

Appendix 13 Acute peripheral vascular event data collection form (pg 8)

FAMILY HISTORY	dad	mum	sib 1	sib 2	sib 3	sib4	sib5
Family history stroke (yes=1, no=2, dk=3)							
Family history MI (code other box age)							
Family history PVD (extent)							
Family history brain haemorrhage							
Family history diabetes (treatment)							
Family history hyperlipidaemia							
Family history hypertension							

Adopted Y / N	
Twin Y / N	

Total number of siblings (include interviewee) ☐

Mother	Alive / dead		Age at death	Cause of death
Father	Alive / dead		Age at death	Cause of death
Sibling 1 (Oldest)	Alive / dead	M / F	Age at death	Cause of death
Sibling 2	Alive / dead	M / F	Age at death	Cause of death
Sibling 3	Alive / dead	M / F	Age at death	Cause of death
Sibling 4	Alive / Dead	M / F	Age at death	Cause of death
Sibling 5 (Youngest)	Alive / Dead	M / F	Age at death	Cause of death

Continue on separate page if necessary

Appendix 13 Acute peripheral vascular event data collection form (pg 9)

Family Tree (number siblings and children)

No of children

History of:	CVA	MI	PVD	ICH	DM	CHOL	HBP
CHILD 1							
CHILD 2							
CHILD 3							
CHILD 4							

Autoimmune History

Y / N / DK	**Personal**	**Family** Number of degree relatives	**Children**
Thyroid			
Early onset diabetes			
Pernicious anaemia			
Rheumatoid arthritis			

Smoking Y / N | lifetime non smoker |

Ex-smoker | age | years smoked |

Current | no / day | years smoked |

Appendix 11 TIA and stroke data collection form (page 12)

Premorbid modified Rankin Y / N

Do you have any symptoms? ☐
Are you able to look after yourself and carry out normal activities? ☐
Does anyone else help pay the bills, do the shopping, cleaning etc? ☐
Do you need someone to help you walk? ☐
Do you need help to wash yourself? ☐
Do you need to be lifted in and out of bed? ☐

0 = no symptoms at all
1 = no significant disability despite symptoms: able to carry out all usual duties and activities
2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3 = moderate disability: requiring some help, but able to walk without assistance
4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6 = death ☐

Rose PVD: IHD questionnaire

Part A

1. Have you ever had any pain or discomfort in your chest? 1=yes 2= no go to part c
2. Do you get the pain or discomfort when you walk up hill or hurry? 1=yes 2=no go to part b
3. Do you get it when you walk at an ordinary pace on the level? 1=yes 2=no
4. When you get any pain or discomfort in your chest what do you do? 1=stop 2=slow down 3=continue at same pace
5. Does it go away when you stand still 1=yes 2=no
6. How soon? 1=10 minutes or less 2= more than 10 minutes

Part B

1. Have you ever had severe pain across the front of your chest lasting half an hour or more? 1=yes 2=no

Part C

1. Do you get pain in either leg when you are walking? 1=yes 2=no (go to next question)
2. Does this pain ever begin when you are standing still or sitting? 1=yes 2=no
3. Do you get this pain in your calf (or calves) 1=yes 2=no
4. Do you get it when you walk up hill or hurry? 1=yes 2=no
5. Do you get it when you walk at an ordinary pace on the level? 1=yes 2=no
6. Does the pain ever disappear while you are still walking? 1=yes 2=no
7. What do you do if you get it when you are walking? 1=stop 2=slow down 3=continue at same pace
8. What happens if you stand still? 1=usually continues for more than 10 minutes 2= usually disappears in 10 minutes or less

Appendix 13 Acute peripheral vascular event data collection form (pg 11)

Pre-morbid Barthel

	Score
Feeding	
0 = unable	
1 = needs help cutting, spreading butter, etc, or requires modified diet	
2 = independent	
Bathing	
0 = dependent	
1 = independent (or in shower)	
Grooming	
0 = needs help with personal care	
1 = independent face/hair/teeth/shaving (implements provided)	
Dressing	
0 = dependent	
1 = needs help but can do about half unaided	
2 = independent (including buttons, zips, laces, etc.)	
Bowels	
0 = incontinent (or needs to be given enemas)	
1 = occasional accident	
2 = continent	
Bladder	
0 = incontinent, or catheterised and unable to manage alone	
1 = occasional accident	
2 = continent	
Toilet use	
0 = dependent	
1 = needs some help, but can do something alone	
2 = independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	
0 = unable, no sitting balance	
1 = major help (one or two people, physical), can sit	
2 = minor help (verbal or physical)	
3 = independent	
Mobility (on level surfaces)	
0 = immobile	
1 = wheelchair independent, including corners, > 50 metres	
2 = walks with help of one person (verbal or physical) > 50 metres	
3 = independent (but may use any aid; for example, stick) > 50 metres	
Stairs	
0 = unable	
1 = needs help (verbal, physical, carrying aid)	
2 = independent	

Barthel score

Appendix 13 Acute peripheral vascular event data collection form (pg 12)

ORIENTATION TO TIME		RESPONSE	SCORE	
What is the...	**year?**	_____	0	1
	season?	_____	0	1
	month of the year?	_____	0	1
	day of the week?	_____	0	1
	date?	_____	0	1
			[ ]	

ORIENTATION TO PLACE*

Where are we now? What is the ...

county?	_____	0	1
city/town/village	_____	0	1
street (suburb)	_____	0	1
house name/number (building name)	_____	0	1
room of house (ward number/level)	_____	0	1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted. [ ]

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready?

Here they are...APPLE *[pause]*, **PENNY** *[pause]*, **TABLE** *[pause]*. **Now repeat those words back to me.** [Repeat up to 5 times, but score only the first trial.]

APPLE	_____	0	1
PENNY	_____	0	1
TABLE	_____	0	1
		[ ]	

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [Serial 7s]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	{93}	_____	0	1
If needed, say: **Keep going.**	{86}	_____	0	1
If needed, say: **Keep going.**	{79}	_____	0	1
If needed, say: **Keep going.**	{72}	_____	0	1
If needed, say: **Keep going.**	{65}	_____	0	1
		_____	[ ]	

Appendix 13 Acute peripheral vascular event data collection form (pg 13)

RESPONSE — SCORE *(circle one)*

Substitute and score this item only if the examinee refuses to perform the Serial 7s task.
Spell the word WORLD forward, then backward, correct forward spelling if misspelled,

but score only the backward spelling

(D = 1) (L = 1) (R = 1) (O = 1) (W = 1) (0-5)

RECALL
What were those three words I asked you to remember? *[Do not offer any hints.]*

APPLE _____ 0 1

PENNY _____ 0 1

TABLE _____ 0 1

NAMING*

What is this? [Point to a pencil or pen.] _____ 0 1

What is this? [Point to a watch] _____ 0 1

*Alternative common objects (e.g. eyeglasses, chair, keys may be substituted and noted.

REPETITION
Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that. [Repeat up to 5 times, but score only the first trial.]

NO IFS, ANDS, OR BUTS. _____ 0 1

COMPREHENSION
Listen carefully because I am going to ask you to do something.
Take this paper in your right hand *[pause]*, **fold it in half** *[pause]*, **and put it on the floor (***or* **table).**

TAKE IN RIGHT HAND _____ 0 1

FOLD IN HALF _____ 0 1

PUT ON FLOOR (*or* TABLE) _____ 0 1

READING
Please read this and do what it says. [*Show the examinee the words on the stimulus form*]

CLOSE YOUR EYES _____ 0 1

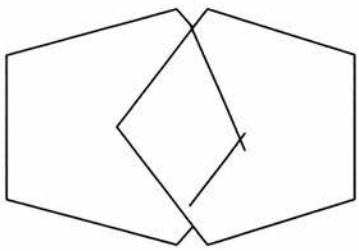
WRITING
Please write a sentence. [*If examinee does not respond, say:* **Write about the weather.**]
Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling. 0 1

DRAWING
Please copy this design. [*Display the intersecting pentagons on the stimulus form.*] 0 1
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

TOTAL SCORE (maximum 30)

Appendix 13 Acute peripheral vascular event data collection form (pg 14)

CLOSE YOUR EYES



Any reason why MMSE is not optimal in this patient?

Onset anger scale

Anger level	Description
1.	**Calm**
2.	**Busy** (but not hassled)
3.	**Mildly angry** (irritated, and hassled, but does not show)
4.	**Moderately angry** (so hassled it shows in your voice)
5.	**Very angry** (body tense, clenching fists or teeth)
6.	**Furious** (almost out of control, very angry, pound table)
7.	**Enraged** (lost control, throwing objects, hurting yourself or

In the two hours prior to the event what best describes your emotional state from the above list (1 – 7)?

In the exact same two hours on the day prior to your event which best describes your mood (1 – 7)?

If you had your event on wakening how were you in the two hours before you went to bed (1 – 7)?

Interviewer's perception of patient personality (see scale below)?

Appendix 13 Acute peripheral vascular event data collection form (pg 15)

In general with regard to stress what kind of person do you think you are? 1=Very relaxed, 2=Fairly relaxed, 3=Average, 4=Prone to stress, 5=Highly stressed

Place of residence: 1=Home, 2=home of relative, 3=home of friend, 4=warden housing, 5=care home, 9=other(specify)

Do you live alone? Y / N

If no with whom

Are you a carer? Y / N
Physical help to wash / dress / transfer or walk

Does anyone assist you at home?
1=Spouse, 2=relative, 3=private carer, 4=community services (specify)

Marital status
married=1, widow=2, single=3, separated=4, partner=5, 9=not k

Contacts with close friends and relatives
How many times do you see a friend or relative each week?
0 – 1 2 – 3 4 – 7 >7

Employment status
Working f/t=1, p/t=2, caring for home=3, unemployed=4, unable to work=5, retired=6, student=7

Most recent occupation
(husband occupation if not employed)

Socioeconomic class (I – VI)

Ethnic origin
1=white, 2=black caribbean, 3=black african, 4=indian, 5=pakistani, 6=bangladeshi, 7=chinese, 8=other

Exercise
Clinician judgement on amount of physical activity (age corrected) per week. 1=None, 2=Below average, 3=Normal, 4=Above average

Alcohol units per week

Education Age left school

1= Basic, 2=Further, 3=Higher

Age left full time education

Appendix 13 Acute peripheral vascular event data collection form (pg 16)

Sleep

What is the likelihood of you dozing in the following situation?

0 = no chance of dozing, 1 = slight chance of dozing,
2 = moderate chance of dozing,3= high chance of dozing

Sitting and reading	0	1	2	3	☐
Lying down to rest in the afternoon when circumstances permit	0	1	2	3	☐
Sitting and talking to someone	0	1	2	3	☐

On average how many hours sleep do you get per night? ☐

Do you snore? Y / N ☐

Have you been told by someone that you stop breathing at night? ☐

Do you take medications for high blood pressure? Y / N ☐

People tell me that I snore
(Use scale below:score 1 – 8) ☐

I have been told by other people that I gasp, choke or snort while I am sleeping ☐
(Use scale below:score 1 – 8)
1=Never, 2=Rarely (1-2X / year), 3=Occasionally (4-8X / year), 4=sometimes (1-2X / month), 5=Often (1-2X / week), 6=Usually (3-5X / week), 7=Always (every night), 8=I don't know

Nutrition

How is your appetite? Good normal poor uncertain ☐

Do you think you have a healthy diet? Y / N / DK ☐

On average how many portions of fish do you eat per week? ☐
1=Less than once per week, 2=once per week, 3=twice a week, 3=>=three times per week

Do you add salt to your food? Y / N ☐

Do you drink full fat (1) or low fat (2) milk ☐

On average how many portions of fresh fruit and vegetables do you eat? 1=Less than once per week, 2=one portion per week, 3=several portions per week, 4=once per day, 5=2-4 portions per day, 6=>=5 portions per day ☐

Appendix 13 Acute peripheral vascular event data collection form (pg 17)

Mood
Do you often feel sad or depressed? Y / N

Driving
Do you drive? Y / N

Handedness
R=Right / L=left / B=both / DK=not known

Clinician impression of frailty (corrected for age)

1=Frail 2=Normal

Life events
Has any of the following unpleasant things happened to you over the last year?
For each answer yes or no Y=1 N=2
Then ask how upset were you by these events?
Very much (1) / moderately (2) / not too much (3)

Death or serious illness of close friend or relative?

Financial difficulty

Divorce or break up of close friends or relatives

Major conflict with children or grandchildren

Muggings / robberies / accidents

Other (specify)

For women

Age of first pregnancy

Number of pregnancies

Age of last pregnancy

Age of menopause

Miscarriage Y / N

Number

OCP Y / N HRT Y / N

No. of years on HRT/OCP

Appendix 13 Acute peripheral vascular event data collection form (pg 18)

General Examination

Collar size (cm)

Waist measurement (cm)

Hip measurement (cm)

Waist / hip ratio

Weight (kg)

Height (m)

BMI

Arcus Y / N

Xanthelasma Y / N

Ear crease Y / N

Nicotine staining Y / N

Own teeth / denture

Temperature on admission (if inpatient)

Pulse on admission
1=Bradycardia (<60) 2=Normal (60 –99) 3=Tachycardia >=100

1=sinus rhythm 2=AF 3=Other

Blood pressure on admissio Sats / air% BM

Pulse at assessment

Blood pressure at assessment

Bruits	Right	Left
Carotid		
Renal		
Femoral		
Subclavian		
Vertebral		

Cardiac murmur Y / N CCF Y /N

Any pre-existing neurological disability? Y / N

Appendix 13 Acute peripheral vascular event data collection form (pg 19)

Critical limb ischaemia ☐

Embolism ☐

Site ☐

Acute on chronic thrombosis ☐

Site ☐

Aneurysm ☐

Site ☐

Rupture ☐ Leak ☐

Other ☐

Site ☐

Appendix 13 Acute peripheral vascular event data collection form (pg 20)

Management

Y / N

Diet

Weight reduction

Smoking

Drug management | New | Continued

Aspirin

Dipyridamole

Clopidogrel

Warfarin

Lipid lowering

Antihypertensive

ACE Inhibitors

Thiazide diuretics

Loop diuretics

Betablockers

Antiarrythmics

LMWH

UFH

Angioplasty

Stent

Surgery

Specify

Appendix 13 Acute peripheral vascular event data collection form (pg 21)

Discharge

Length of stay in acute hospital	
Length of stay rehab hospital	
Total length of stay	
Readmission before 30 days	
Number of readmissions	
30 day case fatality 1=alive 2=dead	

Clinical diagnosis at discharge
Copy immediate discharge letter

Appendix 14 Unstable angina and NSTEMI data collection form (page 1)

ID NO:
Patient identification label

Telephone

Next of kin / contact / relationship
Address

Telephone NOK

Consultant

Examiner

GP Details

Beaumont street	01	East Oxford	03	Berinsfield	04
Malthouse	05	Kidlington	06	Wantage	07
Marcham Rd	08	Stert street	09	Other	10

Summary diagnosis

Non ST elevation MI Y / N

Unstable anginaY/ N

Peak troponin I level

CK rise (>2X) Y / N

ST depression
(>=0.5mm) Y / N
New Q waves Y / N

ST / T wave changes

Is this the first ever in lifetime (incident) ACS? Y / N

Date of notification event
Event leading to notification
Location of interview:
1=JRH in patient / 2=RI in patient / 3=community hospital / 4=outpatients / 5=home / 6=other (specify)

Follow-up plan at 1 month
1=RI TIA clinic / 2=ACS-Primary Care / 3=Refused follow-up / 4=other/ 5=CVA-Primary Care

Information on form obtained from 1=patient / 2=relative / 3=GP / 4=hospital records / 5=death certificate / 6=other

Source of first notification GP=1 / JRH admissions=2 / other hospital=3 / other referrals=4 / health authority search=5 / death=6 / troponin=7/other=9

Other sources of notification(include 1st 2. 3. 4.
Please specify
If one had not identified the patient via the route of first notification would patient been identified by other source of ascertainment? Y / N

Appendix 14 Unstable angina and NSTEMI data collection form (page 2)

History of Notification Event

Narrative history & examination

Typical Ischaemic chest pain – central / radiates / exertonal / relieved GTN – assess rest or exertion >20mins / new onset < 2months / acceleration of severity <2months / change in duration / frequency / angina threshold /

Symptoms Chest pain Y / N ☐ Radiation to arms or neck Y / N ☐

SOB Y / N ☐ Description ☐

Duration of chest pain in minutes ☐

Characteristics of Angina Y / N

More severe ☐ More prolonged ☐

More frequent ☐ Angina at rest ☐

Angina on minimal exertion (lower threshold) ☐

New onset angina within last 2months with minimal exertion ☐

ECG changes compatible with ischaemia Y / N ☐
Transient ST elevation >1mm in 2 contiguous leads,
ST depression, (0.5 / 1.0mm), New Twave inversion of >=1mm,
Pseudonormalisation of previously inverted T waves.

History of, or new, positive exercise test Y / N ☐

Prior or new percutaneous catheterisation (>=50% stenosis) ☐

Prior or new coronary intervention or CABG ☐

Any potential secondary aetiology ☐
Arrhythmia, anaemia, thyroid disease, sepsis, surgery:
Please specify

☐

Appendix 14 Unstable angina and NSTEMI data collection form (page 3)

Notification event date | | | | | | time | | | |
(The event that led to GP notification)

What did you think was wrong?

Were you alone? Y / N | |

If you were with someone who was it? | |

Who called for help? | |

If you did not call for help at time of event, why not?

Who did you (or person with you) first call for help? 1=medical / 2=non medical | |

First call for help date | | | | | | time | | | |
(if medical code '9s')

First call to GP / A&E date | | | | | | time | | | |
/ 999 i.e medical

Outcome of first call for medical assistance

Seen by GP / A&E date | | | | | | time | | | |

GP notification to date | | | | | | time | | | |
OXVASC/ascertainment

Admission (if admitted) date | | | | | | time | | | |

Assessment date | | | | | | time | | | |

Appendix 14 Unstable angina and NSTEMI data collection form (pg4)

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	NSTEMI or STEMI	Cerebral TIA CVA	Peripheral
Number of events			
Date of most recent			

Background Medical History

Angina Y / N ☐ Age at diagnosis ☐

Hypertension Y / N ☐ Age at diagnosis ☐

Myocardial infarction Y / N ☐ Age at diagnosis ☐

Diabetes mellitus Y / N ☐ Age at diagnosis ☐

Treatment: Diet ☐ Tablets Y / N ☐

Insulin Y / N ☐

Valvular heart disease Y / N ☐ Age at diagnosis ☐

Nature: ☐

Intermittent claudication Y / N ☐ Age at diagnosis ☐

Peripheral vascular intervention

Y / N ☐ Age at first intervention ☐

Site:

Type: angiogram ☐ angioplasty ☐ bypass ☐ amputation ☐

Result ☐

Appendix 14 Unstable angina and NSTEMI data collection form (pg5)

Atrial fibrillation Y / N ☐ Age at diagnosis ☐

1=Current / 2=Previous ☐

1=Cardioversion, 2=paroxsymal, 3=persistent, 4=permanent ☐

Pacemaker Y / N ☐ Type ☐

Hyperlipidaemia Y / N / DK ☐ Age at diagnosis ☐

Treatment: Diet Y / N ☐ Statin Y / N ☐ Other ☐

Cardiac failure Y / N ☐ Age at diagnosis ☐ Treated ☐

Migraine Y / N ☐ With aura Y / N ☐

Prolonged aura (>1h) Y / N ☐

Epilepsy Y / N ☐ Age at diagnosis ☐

Cardiac intervention Y / N ☐ age at first interventic ☐

Angiogram ☐ angioplasty ☐ stent ☐ bypass ☐

Result angiogram
LM / LAD / LCx / RCA
Mild < 50%
Moderate 51–59%
Severe >60%
Bypass grafts ☐

Carotid endarterectomy Y / N ☐ Age at operation ☐ Side ☐

Asthma Y / N ☐ **Liver disease** Y / N ☐

COAD Y / N ☐ **Peptic ulcer disease** ☐

Appendix 14 Unstable angina and NSTEMI data collection form (pg 6)

Any previous venous thromboses Y / N ☐ Number ☐
Give details below

☐

Any other past medical history ☐

SLE (look in notes) Y / N ☐ Age of diagnosis ☐

Anticardiolipin antibodies (aCL) Y / N / DK ☐

Lupus anticoagulant (LA) Y / N / DK ☐

Autoimmune disease Y / N ☐
If so give diagnosis:

☐

Allergies ☐

Nosebleeds Y / N ☐ **Bleeding after dental extraction** Y / N ☐

Any cancer ☐ **End stage renal failure / dialysis** ☐

List of medications <u>before onset</u> of notification event

Aspirin Y / N ☐ Dose ☐

Dipyridamole Y / N ☐

Clopidogrel Y / N ☐

Warfarin Y / N ☐ INR ☐

Appendix 14 Unstable angina and NSTEMI data collection form (pg 7)

Aspirin Resistance (ask re drugs in 10 days prior to assessment)

Were you on aspirin before this event? Y/N ☐ Date started? ☐

Have you had aspirin since this acute event? Y/N ☐

What doses? (date & dose) ☐

Were you on clopidogrel before this event? Y / N ☐ Date started? ☐

Have you had clopidogrel since this acute event? Y / N ☐

What doses? (date & dose) ☐

Have you had any anti inflammatories in 10 days prior to assessment? Y / N ☐

What drug and doses? ☐

Do you take vitamin supplements? Y / N ☐

B6 Y / N ☐ FOLATE Y / N ☐ B12 Y / N ☐

List names of supplements

☐

Other medication : *scroll of other drugs on database*

☐

Was your BP measured at any time prior to the notification event? ☐

Date of most recent BP measurement prior to notification event ☐

How many times have you had your BP measured in the last year? ☐

Over the last 10 years how many times have you had your BP measured? 1=none, 2=one to two times, 3=three to five times, 4=more than five times, 9=don't know ☐

Previous stroke or TIA Since 1/4/02		date recent	previous yes	previous no	no of events	date 1st event	duration recent	duration longest
Hemispheric stroke carotid	right						xxx	xxxxx
	left						xxx	xxxxx
Hemisheric TIA carotid	right							
	left							
Vertebrobasilar stroke							xxx	xxxxx
Vertebrobasilar TIA								
Stroke unknown territory							xxx	xxxxx
TIA unknown territory								
Amaurosis fugax	right							
	left							
Retinal infarction	right						xxx	xxxxx
	Left						xxx	xxxx

Appendix 14 Unstable angina and NSTEMI data collection form (pg 8)

FAMILY HISTORY	dad	mum	sib 1	sib 2	sib 3	sib4	sib5
Family history stroke (yes=1, no=2, dk=3)							
Family history MI (code other box age)							
Family history PVD (extent)							
Family history brain haemorrhage							
Family history diabetes (treatment)							
Family history hyperlipidaemia							
Family history hypertension							

Adopted Y / N	
Twin Y / N	

Appendix 14 Unstable angina and NSTEMI data collection form (pg 9)

Total number of siblings (include interviewee) ☐

Mother	Alive / dead		Age at death	Cause of death
Father	Alive / dead		Age at death	Cause of death
Sibling 1 (Oldest)	Alive / dead	M / F	Age at death	Cause of death
Sibling 2	Alive / dead	M / F	Age at death	Cause of death
Sibling 3	Alive / dead	M / F	Age at death	Cause of death
Sibling 4	Alive / Dead	M / F	Age at death	Cause of death
Sibling 5 (Youngest)	Alive / Dead	M / F	Age at death	Cause of death

Continue on separate page if necessary

Family Tree (number siblings and children)

Appendix 14 Unstable angina and NSTEMI data collection form (pg 9-10)

No of children ☐

History of:	CVA	MI	PVD	ICH	DM	CHOL	HBP
CHILD 1							
CHILD 2							
CHILD 3							
CHILD 4							

Autoimmune History

Y / N / DK	**Personal**	**Family** Number of degree relatives	**Children**
Thyroid			
Early onset diabetes			
Pernicious anaemia			
Rheumatoid arthritis			

Smoking Y / N ☐ lifetime non smoker ☐

Ex-smoker ☐ age ☐ years smoked ☐

Current ☐ no / day ☐ years smoke ☐

Appendix 14 Unstable angina and NSTEMI data collection form (pg 10)

<u>Premorbid</u> modified Rankin Y / N

Do you have any symptoms? ☐
Are you able to look after yourself and carry out normal activities? ☐
Does anyone else help pay the bills, do the shopping, cleaning etc? ☐
Do you need someone to help you walk? ☐
Do you need help to wash yourself? ☐
Do you need to be lifted in and out of bed? ☐

0 = no symptoms at all
1 = no significant disability despite symptoms: able to carry out all usual duties and activities
2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3 = moderate disability: requiring some help, but able to walk without assistance
4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6 = death ☐

Appendix 14 Unstable angina and NSTEMI data collection form (pg 11)

Rose PVD: IHD questionnaire

Part A

1. Have you ever had any pain or discomfort in your chest? 1=yes 2= no go to part c
2. Do you get the pain or discomfort when you walk up hill or hurry? 1=yes 2=no go to part b
3. Do you get it when you walk at an ordinary pace on the level? 1=yes 2=no
4. When you get any pain or discomfort in your chest what do you do? 1=stop 2=slow down 3=continue at same pace
5. Does it go away when you stand still 1=yes 2=no
6. How soon? 1=10 minutes or less 2= more than 10 minutes

Part B

1. Have you ever had severe pain across the front of your chest lasting half an hour or more? 1=yes 2=no

Part C

1. Do you get pain in either leg when you are walking? 1=yes 2=no (go to next question)
2. Does this pain ever begin when you are standing still or sitting? 1=yes 2=no
3. Do you get this pain in your calf (or calves) 1=yes 2=no
4. Do you get it when you walk up hill or hurry? 1=yes 2=no
5. Do you get it when you walk at an ordinary pace on the level? 1=yes 2=no
6. Does the pain ever disappear while you are still walking? 1=yes 2=no
7. What do you do if you get it when you are walking? 1=stop 2=slow down 3=continue at same pace
8. What happens if you stand still? 1=usually continues for more than 10 minutes 2= usually disappears in 10 minutes or less

Appendix 14 Unstable angina and NSTEMI data collection form (pg 12)

Pre-morbid Barthel

	Score
Feeding	
0 = unable	
1 = needs help cutting, spreading butter, etc, or requires modified diet	
2 = independent	
Bathing	
0 = dependent	
1 = independent (or in shower)	
Grooming	
0 = needs help with personal care	
1 = independent face/hair/teeth/shaving (implements provided)	
Dressing	
0 = dependent	
1 = needs help but can do about half unaided	
2 = independent (including buttons, zips, laces, etc.)	
Bowels	
0 = incontinent (or needs to be given enemas)	
1 = occasional accident	
2 = continent	
Bladder	
0 = incontinent, or catheterised and unable to manage alone	
1 = occasional accident	
2 = continent	
Toilet use	
0 = dependent	
1 = needs some help, but can do something alone	
2 = independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	
0 = unable, no sitting balance	
1 = major help (one or two people, physical), can sit	
2 = minor help (verbal or physical)	
3 = independent	
Mobility (on level surfaces)	
0 = immobile	
1 = wheelchair independent, including corners, > 50 metres	
2 = walks with help of one person (verbal or physical) > 50 metres	
3 = independent (but may use any aid; for example, stick) > 50 metres	
Stairs	
0 = unable	
1 = needs help (verbal, physical, carrying aid)	
2 = independent	

Barthel score

Appendix 14 Unstable angina and NSTEMI data collection form (pg 13)

Onset anger scale

Anger level	Description
8	**Calm**
9	**Busy** (but not hassled)
10	**Mildly angry** (irritated, and hassled, but does not show)
11	**Moderately angry** (so hassled it shows in your voice)
12	**Very angry** (body tense, clenching fists or teeth)
13	**Furious** (almost out of control, very angry, pound table)
14	**Enraged** (lost control, throwing objects, hurting yourself or

In the two hours prior to the event what best describes your emotional state from the above list (1 – 7)? ☐

In the exact same two hours on the day prior to your event which best describes your mood (1 – 7)? ☐

If you had your event on wakening how were you in the two hours before you went to bed (1 – 7)? ☐

Interviewer's perception of patient personality (see scale below)? ☐

In general with regard to stress what kind of person do you think you are? 1=Very relaxed, 2=Fairly relaxed, 3=Average, 4=Prone to stress, 5=Highly stressed ☐

Place of residence: 1=Home, 2=home of relative, 3=home of friend, 4=warden housing, 5=care home, 9=other(specify) ☐

Do you live alone? Y / N ☐ If no with whom ☐

Are you a carer? Y / N
Physical help to wash / dress / transfer or walk ☐

Does anyone assist you at home?
1=Spouse, 2=relative, 3=private carer, 4=community services (specify) ☐

Marital status
married=1, widow=2, single=3, separated=4, partner=5, 9=not know ☐

Appendix 14 Unstable angina and NSTEMI data collection form (pg 14)

Contacts with close friends and relatives
How many times do you see a friend or relative each week?
0 – 1 2 – 3 4 – 7 >7 ☐

Employment status
Working f/t=1, p/t=2, caring for home=3,
unemployed=4, unable to work=5, retired=6, student=7 ☐

Most recent occupation
(husband occupation if not employed) ☐

Socioeconomic class (I – VI) ☐

Ethnic origin
1=white, 2=black caribbean, 3=black african, 4=indian,
5=pakistani, 6=bangladeshi, 7=chinese, 8=other ☐

Exercise
Clinician judgement on amount of physical activity
(age corrected) per week. 1=None, 2=Below average,
3=Normal, 4=Above average ☐

Alcohol units per week ☐

Education Age left school ☐ 1= Basic, 2=Further, 3=Higher ☐

Age left full time education ☐

Nutrition
How is your appetite? Good normal poor uncertain ☐

Do you think you have a healthy diet? Y / N / DK ☐

On average how many portions of fish do you eat per week?
1=Less than once per week, 2=once per week, 3=twice a week,
3=>=three times per week ☐

Do you add salt to your food? Y / N ☐

Do you drink full fat (1) or low fat (2) milk ☐

On average how many portions of fresh fruit
and vegetables do you eat? 1=Less than once per week, 2=one
portion per week, 3=several portions per week, 4=once per day,
5=2-4 portions per day, 6=>=5 portions per day ☐

Appendix 14 Unstable angina and NSTEMI data collection form (pg 15)

Mood
Do you often feel sad or depressed? Y / N

Driving
Do you drive? Y / N

Handedness
R=Right / L=left / B=both / DK=not known

Clinician impression of frailty (corrected for age)

1=Frail 2=Normal

Life events
Has any of the following unpleasant things happened to you over the last year?
For each answer yes or no Y=1 N=2
Then ask how upset were you by these events?
Very much (1) / moderately (2) / not too much (3)

Death or serious illness of close friend or relative?

Financial difficulty

Divorce or break up of close friends or relatives

Major conflict with children or grandchildren

Muggings / robberies / accidents

Other (specify)

For women

Age of first pregnancy

Number of pregnancies

Age of last pregnancy

Age of menopause

Miscarriage Y / N

Number

OCP Y / N

HRT Y / N

No. of years on HRT/OCP

Appendix 14 Unstable angina and NSTEMI data collection form (pg 16)

Investigations

Cardiac enzymes

	CK	peak	AST	LDH	troponin	peak
Dates Admission						
Day 1						
Day 2						
Day 3						

Coded ECG 1=AF 2=BBB 3=STsegment change 4=LVH ☐
5=Acute MI 6=Old MI 7=Normal 9=Other
Need copies

For NSTEMI
TIMI – NSTEMI Score

Age >=65 = 1 ☐

>=3 CAD Risk factors = 1 ☐
FHx HBP Raised chol DM

Known CAD = 1 ☐
Stenosis>=50%

ASA use in past 7 days =1 ☐

Recent (<=24h) severe angina = 1 ☐

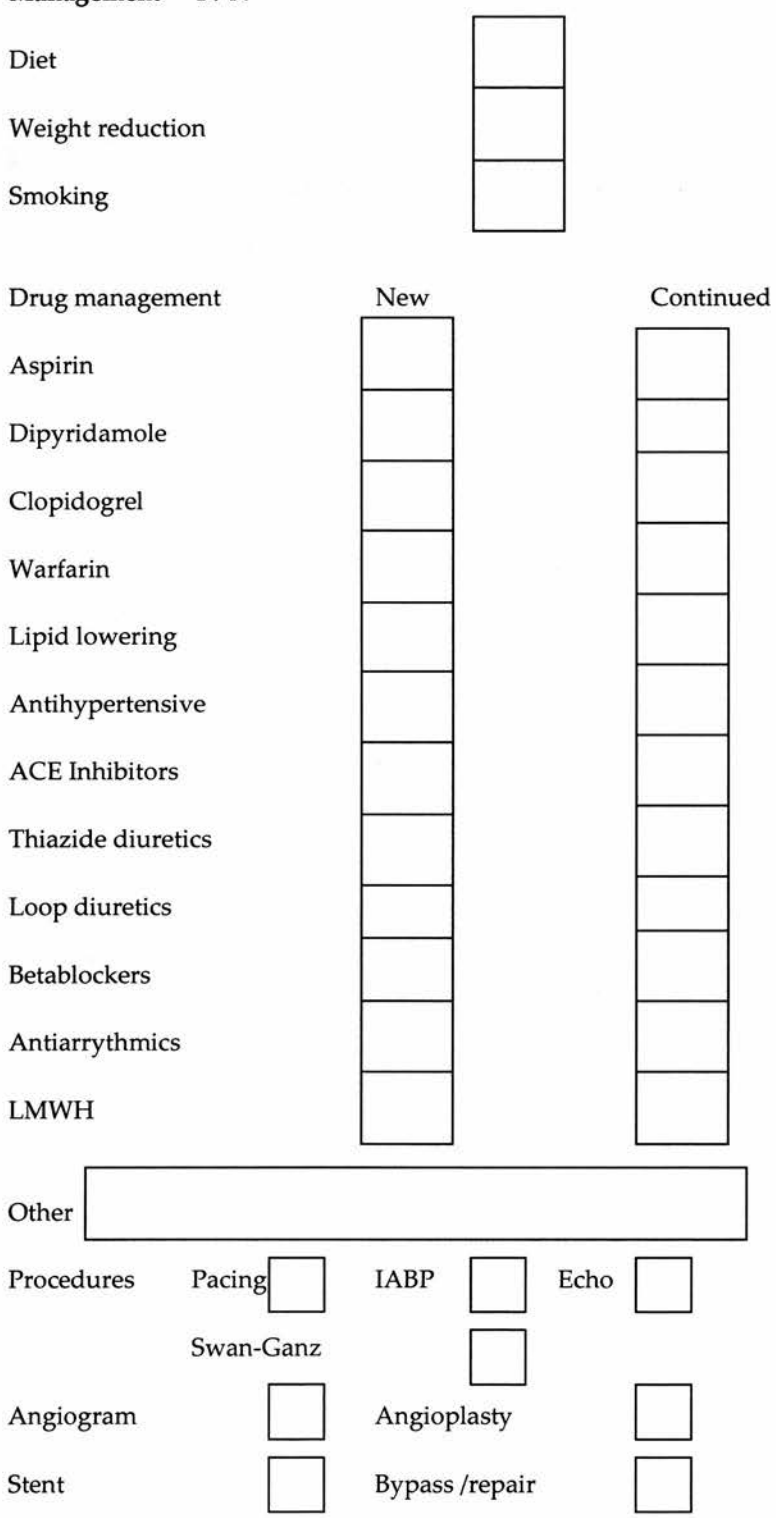
Raised cardiac markers = 1 ☐

ST deviation >=0.5mm = 1 ☐

TIMI – score NSTEMI ☐

Notes

Appendix 14 Unstable angina and NSTEMI data collection form (pg 17)



Appendix 14 Unstable angina and NSTEMI data collection form (pg 18)

Discharge

Length of stay in acute hospital ☐

Length of stay rehab hospital ☐

Total length of stay ☐

Readmission before 30 days ☐

Number of readmissions ☐

30 day case fatality 1=alive 2=dead ☐

Clinical diagnosis at discharge
Copy immediate discharge letter

Diagnosis after review by Dr Banning

Acute coronary syndrome Y/N ☐

Unstable angina ☐

NSTEMI ☐

STEMI ☐

Non – cardiac ☐ Stable angina ☐

Appendix 15 Vascular intervention data collection form (page 1)

ID NO:

Patient identification label

Telephone

Next of kin / contact / relationship

Telephone NOK

Address

Consultant

Examiner

GP Details

Beaumont street	01	East Oxford	03	Berinsfield	04	
Malthouse	05	Kidlington	06	Wantage	07	
Marcham Rd	08	Stert street	09	Other	10	

Summary diagnosis

Angiography	1=coronary	2=cerebral	3=peripheral	
Angioplasty	1=coronary	2=peripheral		
Stent	1=coronary	2=cerebral	3=peripheral	
Surgery	1=CABG	2=CEA	3=peripheral (specify)	

Other: specify

Is this the first ever (incident) vascular intervention event? Y / N

Date of notification event

Event leading to notification

Location of interview:

1=JRH in patient / 2=RI in patient / 3=community hospital / 4=outpatients / 5=home / 6=other (specify)

Follow-up plan at 1 month

1=RI TIA clinic / 2=ACS-Primary Care / 3=Refused follow-up / 4=other/ 5=CVA-Primary Care

Information on form obtained from 1=patient / 2=relative / 3=GP / 4=hospital records / 5=death certificate / 6=other

Source of first notification GP=1 / JRH admissions=2 / other hospital=3 / other referrals=4 / health authority search=5 / death=6 / troponin=7/other=9

Other sources of notification(include 1st 2. 3. 4.

Please specify

If one had not identified the patient via the route of first notification would patient been identified by other source of ascertainment? Y / N

Appendix 15 Vascular intervention data collection form (page 2)

Narrative history & examination

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	NSTEMI or STEMI	Cerebral TIA CVA	Peripheral
Number of events			
Date of most recent			

Angina Y / N ☐ Age at diagnosis ☐

Hypertension Y / N ☐ Age at diagnosis ☐

Myocardial infarction Y / N ☐ Age at diagnosis ☐

Diabetes mellitus Y / N ☐ Age at diagnosis ☐

Treatment: Diet Y / N ☐ Tablets Y / N ☐

Insulin Y / N ☐

Valvular heart disease Y / N ☐ Age at diagnosis ☐

Nature: ☐

Intermittent claudication Y / N ☐ Age at diagnosis ☐

Peripheral vascular intervention

Y / N ☐ Age at first intervention ☐

Site:

Type: angiogram ☐ angioplasty ☐ bypass ☐ amputation ☐

Result ☐

Appendix 15 Vascular intervention data collection form (page 3)

Atrial fibrillation Y / N Age at dia

1=Current / 2=Previous

1=Cardioversion, 2=paroxsymal, 3=persistent, 4=permanent

Pacemaker Y / N Type

Hyperlipidaemia Y / N / DK Age at diagnosis

Treatment: Diet Y / N Statin Y / N Other

Cardiac failure Y / N Age at diagnosis Treated

Migraine Y / N With aura Y / N

Prolonged aura (>1h) Y / N

Epilepsy Y / N Age at diagnosis

Cardiac intervention Y / N age at first interventic

Angiogram angioplasty stent bypass

Result angiogram
LM / LAD / LCx / RCA
Mild < 50%
Moderate 51–59%
Severe >60%
Bypass grafts

Carotid endarterectomy Y / N Age at operation Side

Asthma Y / N
COAD Y / N
Liver disease Y / N
Peptic ulcer disease

Any previous venous thromboses Y / N No.
Give details below

Appendix 15 Vascular intervention data collection form (page 4)

Any other past medical history

SLE (look in notes) Y / N Age of diagnosis

Anticardiolipin antibodies (aCL) Y / N / DK

Lupus anticoagulant (LA) Y / N / DK

Autoimmune disease Y / N
If so give diagnosis:

Allergies

Nosebleeds Y / N **Bleeding after dental extraction** Y / N

Any cancer **End stage renal failure / dialysis**

List of medications before onset of notification event

Aspirin Y / N Dose

Dipyridamole Y / N

Clopidogrel Y / N

Warfarin Y / N INR

Do you take vitamin supplements? Y / N

B6 Y / N FOLATE Y / N B12 Y / N

List names of supplements

Other medication : *scroll of other drugs on database*

Appendix 15 Vascular intervention data collection form (page 5)

Previous stroke or TIA Since 1/4/02		date recent	previous yes	previous no	no of events	date 1st event	duration recent	duration longest
Hemispheric stroke carotid	right						xxx	xxxxx
	left						xxx	xxxxx
Hemisheric TIA carotid	right							
	left							
Vertebrobasilar stroke							xxx	xxxxx
Vertebrobasilar TIA								
Stroke unknown territory							xxx	xxxxx
TIA unknown territory								
Amaurosis fugax	right							
	left							
Retinal infarction	right						xxx	xxxxx
	Left						xxx	xxxx

Appendix 15 Vascular intervention data collection form (page 5)

FAMILY HISTORY	dad	mum	sib 1	sib 2	sib 3	sib4	sib5
Family history stroke (yes=1, no=2, dk=3)							
Family history MI (code other box age)							
Family history PVD (extent)							
Family history brain haemorrhage							
Family history diabetes (treatment)							
Family history hyperlipidaemia							
Family history hypertension							

Adopted Y / N	
Twin Y / N	

Appendix 15 Vascular intervention data collection form (page 6)

Total number of siblings (include interviewee) ☐

Mother	Alive / dead		Age at death	Cause of death
Father	Alive / dead		Age at death	Cause of death
Sibling 1 (Oldest)	Alive / dead	M / F	Age at death	Cause of death
Sibling 2	Alive / dead	M / F	Age at death	Cause of death
Sibling 3	Alive / dead	M / F	Age at death	Cause of death
Sibling 4	Alive / Dead	M / F	Age at death	Cause of death
Sibling 5 (Youngest)	Alive / Dead	M / F	Age at death	Cause of death

Continue on separate page if necessary

Appendix 15 Vascular intervention data collection form (page 6-7)

Family Tree (number siblings and children)

No of children ☐

History of:	CVA	MI	PVD	ICH	DM	CHOL	HBP
CHILD 1							
CHILD 2							
CHILD 3							
CHILD 4							

Autoimmune History

Y / N / DK	**Personal**	**Family** Number of degree relatives	**Children**
Thyroid			
Early onset diabetes			
Pernicious anaemia			
Rheumatoid arthritis			

Smoking Y / N ☐ lifetime non smoker ☐

Ex-smoker ☐ age ☐ years smoked ☐

Current ☐ no / day ☐ years smoke ☐

Appendix 15 Vascular intervention data collection form (page 7)

Interviewer's perception of patient personality (see scale below)? ☐

In general with regard to stress what kind of
person do you think you are? 1=Very relaxed,
2=Fairly relaxed, 3=Average, 4=Prone to stress, 5=Highly stressed ☐

Place of residence: 1=Home, 2=home of relative,
3=home of friend, 4=warden housing,
5=care home, 9=other(specify) ☐

Do you live alone? Y / N ☐ If no with whom ☐

Are you a carer? Y / N ☐
Physical help to wash / dress / transfer or walk

Does anyone assist you at home?
1=Spouse, 2=relative, 3=private carer,
4=community services (specify) ☐

Marital status ☐
married=1, widow=2, single=3, separated=4, partner=5,
9=not known

Contacts with close friends and relatives ☐
How many times do you see a friend or relative each week?
0 – 1 2 – 3 4 – 7 >7

Appendix 15 Vascular intervention data collection form (page 8)

Employment status
Working f/t=1, p/t=2, caring for home=3,
unemployed=4, unable to work=5, retired=6, student=7

Most recent occupation
(husband occupation if not employed)

Socioeconomic class (I – VI)

Ethnic origin
1=white, 2=black caribbean, 3=black african, 4=indian,
5=pakistani, 6=bangladeshi, 7=chinese, 8=other

Exercise
Clinician judgement on amount of physical activity
(age corrected) per week. 1=None, 2=Below average,
3=Normal, 4=Above average

Alcohol units per week

Education Age left school

1= Basic,
2=Further,
3=Higher

Age left full time education

Nutrition
How is your appetite? Good normal poor uncertain

Do you think you have a healthy diet? Y / N / DK

On average how many portions of fish do you eat per week?
1=Less than once per week, 2=once per week, 3=twice a week,
3=>=three times per week

Do you add salt to your food? Y / N

Do you drink full fat (1) or low fat (2) milk

On average how many portions of fresh fruit
and vegetables do you eat? 1=Less than once per week, 2=one
portion per week, 3=several portions per week, 4=once per day,
5=2-4 portions per day, 6=>=5 portions per day

Mood, Do you often feel sad or depressed? Y / N

Driving Do you drive? Y / N

Appendix 15 Vascular intervention data collection form (page 9)

Handedness
R=Right / L=left / B=both / DK=not known

Clinician impression of frailty (corrected for age)

1=Frail 2=Normal

Life events
Has any of the following unpleasant things happened to you over the last year?
For each answer yes or no Y=1 N=2
Then ask how upset were you by these events?
Very much (1) / moderately (2) / not too much (3)

Death or serious illness of close friend or relative?

Financial difficulty

Divorce or break up of close friends or relatives

Major conflict with children or grandchildren

Muggings / robberies / accidents

Other (specify)

For women

Age of first pregnancy

Number of pregnancies

Age of last pregnancy

Age of menopause

Miscarriage Y / N

Number

OCP Y / N

HRT Y / N

No. of years on HRT/OCP

Pre-morbid Barthel

	Score
Feeding	
0 = unable	
1 = needs help cutting, spreading butter, etc, or requires modified diet	
2 = independent	
Bathing	
0 = dependent	
1 = independent (or in shower)	
Grooming	
0 = needs help with personal care	
1 = independent face/hair/teeth/shaving (implements provided)	
Dressing	
0 = dependent	
1 = needs help but can do about half unaided	
2 = independent (including buttons, zips, laces, etc.)	
Bowels	
0 = incontinent (or needs to be given enemas)	
1 = occasional accident	
2 = continent	
Bladder	
0 = incontinent, or catheterised and unable to manage alone	
1 = occasional accident	
2 = continent	
Toilet use	
0 = dependent	
1 = needs some help, but can do something alone	
2 = independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	
0 = unable, no sitting balance	
1 = major help (one or two people, physical), can sit	
2 = minor help (verbal or physical)	
3 = independent	
Mobility (on level surfaces)	
0 = immobile	
1 = wheelchair independent, including corners, > 50 metres	
2 = walks with help of one person (verbal or physical) > 50 metres	
3 = independent (but may use any aid; for example, stick) > 50 metres	
Stairs	
0 = unable	
1 = needs help (verbal, physical, carrying aid)	
2 = independent	

Barthel score

Appendix 15 Vascular intervention data collection form (page 11)

<u>Premorbid</u> modified Rankin Y / N

Do you have any symptoms? ☐
Are you able to look after yourself and carry out normal activities? ☐
Does anyone else help pay the bills, do the shopping, cleaning etc? ☐
Do you need someone to help you walk? ☐
Do you need help to wash yourself? ☐
Do you need to be lifted in and out of bed? ☐

0 = no symptoms at all
1 = no significant disability despite symptoms: able to carry out all usual duties and activities
2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3 = moderate disability: requiring some help, but able to walk without assistance
4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6 = death ☐

Comments

Appendix 16 Troponin > 1 data collection form (page 1)

ID NO:
Patient identification label

Telephone

Next of kin / contact / relationship
Address

Telephone NOK

Consultant

Examiner

GP Details

Beaumont street	01	East Oxford	03	Berinsfield	04	
Malthouse	05	Kidlington	06	Wantage	07	
Marcham Rd	08	Stert street	09	Other	10	

Summary of events and diagnosis (Presentation, timing, diagnosis, comments)

Date of notification event

Methods of ascertainment

Previous TIA

Previous stroke

Angina

Hypertension

Previous ACS / MI

Atrial fibrillation

Diabetes mellitus

Diet

Tablets

Insulin

Valvular heart disease

Intermittent claudication

Previous peripheral angiogram

Appendix 16 Troponin > 1 data collection form (page 2)

Pacemaker ☐ Migraine ☐

Hyperlipidaemia ☐ Diet ☐ Statin ☐ Other ☐

Cardiac failure ☐ Previous coronary angiogram ☐

Previous CABG ☐ Carotid endarterectomy ☐

Epilepsy ☐ Allergies ☐

Asthma ☐ Liver disease ☐

COAD ☐ Peptic ulcer disease ☐

Any previous venous thromboses ☐ Any malignancy ☐

Autoimmune disease (thyroid, RA, PA etc) ☐ ☐

Any other relevant past medical history ☐

List of medications <u>before onset</u> of notification event

Aspirin ☐ Dipyridamole ☐ Clopidogrel ☐ Warfarin ☐

Statin ☐ BP lowering ☐ Other ☐

Current smoker ☐ Lifetime non smoker ☐ Ex-smoker ☐

Any family history ☐

Peak troponin level ☐ CK ☐ AST ☐

ECG changes (ST depression / ST-T) ☐ ECG Report 1. ☐ 2. ☐

Final diagnosis ☐

Cause of death (if applicable) Date ☐ Coroner / PM ☐

Ia

IIb

II

Appendix 17 Brain imaging data collection form (Page 1)

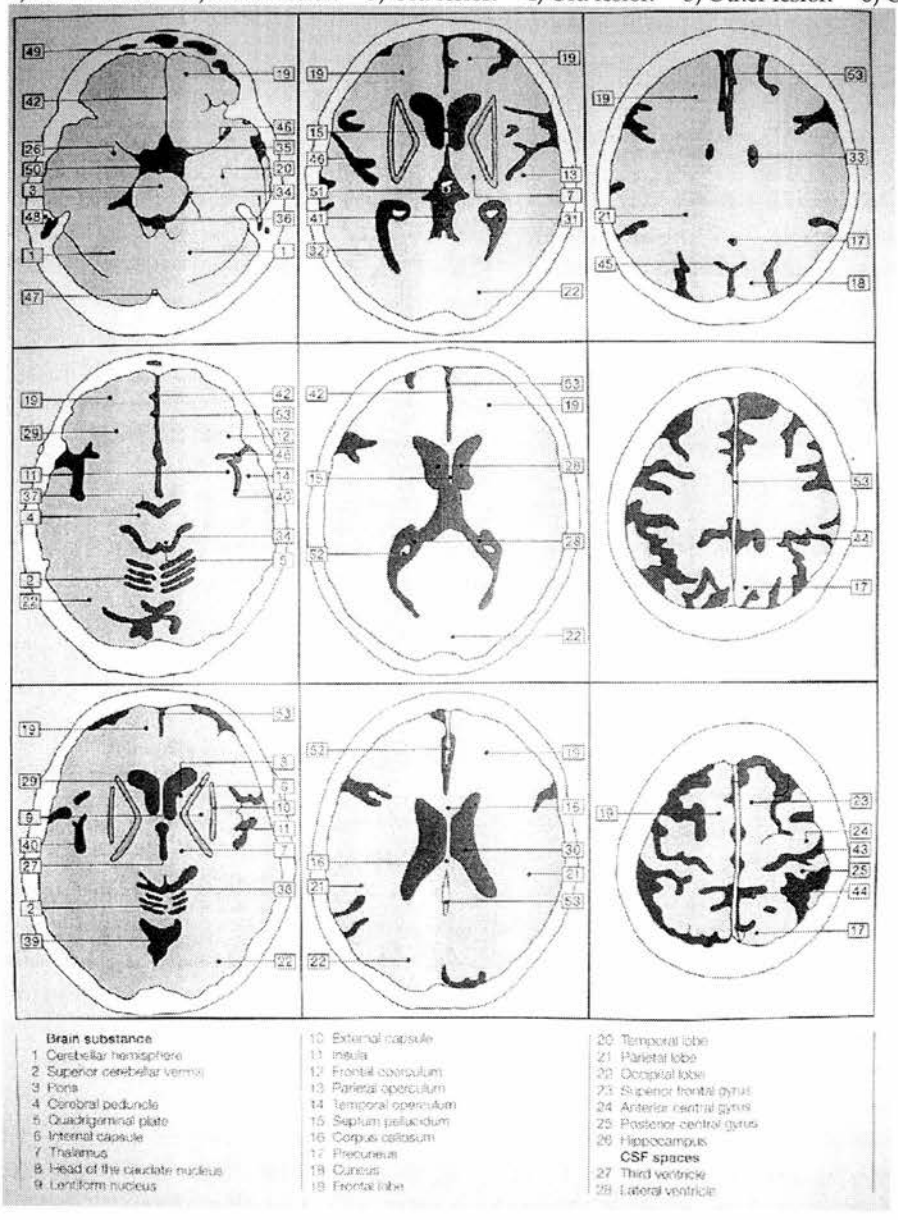
OXVASC ID No.

Date of scan ☐ Days from notification event ☐

CT done Y / N ☐ MRI Y / N ☐ If not why? ☐

Describe main lesions

1) Acute lesion 2) Acute lesion 3) Old lesion 4) Old lesion 5) Other lesion 6) Others



Appendix 17 Brain imaging data collection form (Page 2)

Scan quality
1=Good/ 2= Poor quality, diagnostic/ 3=Poor quality, nondiagnostic/ 4=not relevant ☐

	1	2	3	4	5
	Acute	Acute	Old	Old	Other
Lesion 1=Stroke lesion, 2=non stroke lesion, 3=normal, 4= abnormal, 9=uncertain					
Signs for acute lesions 1=Appropriate to signs, 2=inappropriate, 9=uncertain					
Pathology 1=Infarct, 2= definite PICH, 3= definite infarct with haemorrhagic transformation, 4=SAH, 9=uncertain					
Side 1=right, 2=left, 3=midline, 9=uncertain					
Territory 1=Posterior, 2=deep anterior, 3=superficial anterior, 4=both, 5=watershed					
For cerebral infarct 1=No haemorrhagic transformation, 2=Haemorrhagic transformation without haematoma, 3=Haemorrhagic transformation with haematoma, 4=Haemorrhagic transformation with intraventricular blood, 9=primary intracerebral haemorrhage					
For primary intracerebral haemorrhage 1=Intraventricular blood, 2=No intraventricular blood, 3=Uncertain, 9=cerebral infarct					
Amount of haematoma 1=Petechial haemorrhage, 2=up to 2cm, 3=2cm and over, 9=uncertain					
Mass effect 0=Scarring and ventricular dilatation/ 1=No swelling / 2=Effacement sulci over infarct 3=Minor effacement adjacent lateral ventricle 4=Complete effacement of the lateral ventricle 5=Effacement of lateral and third ventricle 6=Shift of midline away from side of ventricle 7=Effacement of the basal cisterns					

Periventricular white matter lucencies Y / N ☐ Mild/ Moderate/ Severe ☐

Atrophy for age Y/ N Cortical/ Central/ Cortical and central/ Cerebellar ☐
Focal/ Diffuse ☐
Mild/ Moderate/ Severe ☐

Change of radiological diagnosis after unblinding Y/ N ☐

What was the change? ☐

Appendix 18 Follow-up protocol

	TIA and non-PVD hospitalised stroke	**Hospitalised stroke**	**Acute coronary syndrome**
1m	SPRU Clinic/Home	Primary Care Hospital/home	PrimaryCare Home
3m	Primary Care Home	Primary Care Home	Primary Care Home
6m	Primary Care Home	Primary Care Home	Primary Care Telephone
12m	SPRU Clinic	SPRU Clinic/home	Primary Care Home

Appendix 19 Follow-up data collection form

OXREC: CO2.043 **OXVASC** **ID No.**

Date **Follow up**

Circle **1** **3** **6** **9** **12**

Recurrent Events	1 = yes 2 = no	Number of events	Date of event	Comments
Chest pain (requiring admission)				
TIA (<24h sudden onset focal neurological disturbance)				
Stroke (>24h)				
Acute PVD event (eg embolus, aneurysm)				

Cardiac procedure	1 = yes, 2 = no	No. of events	Date of event	Comments
Angiogram				
Angioplasty				
Stent				
CABG				
Carotid procedure				
Carotid endarterectomy				
Peripheral procedure				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				
Other procedures/ Surgery (Please specify)				

Smoking Y / N

BP

Seizures (treated) Y / N

Rankin (0 – 6)

MMSE (/30)

Driving Y / N

Working Y / N

Depression (treated) Y / N

Barthel (/ 20)

Survival Y / N

Screen for TIA / Stroke: Have you had any sudden onset of severe headache, visual loss, speech disturbance, double vision, slurred speech, weakness or numbness of face,arm or leg?

Appendix 20 Recurrent event data collection form (page 1)

ID NO: ☐☐☐☐☐

Patient identification label

Date of Notification Event

GP Details

Beaumont street	01	East Oxford	03	Berinsfield	04	
Malthouse	05	Kidlington	06	Wantage	07	
Marcham Rd	08	Stert street	09	Other	10	

Date of recurrent event

Acute vascular recurrent event

Chest pain (requiring admission)	Unstable angina	NSTEMI	STEMI	Y/N
No chest pain troponin > 1				
TIA (<24h sudden onset focal neurological disturbance)				
Stroke (>24h)				
Acute PVD event (eg embolus, aneurysm)				
Death				

Summary history of recurrent event

Include date of presentation, medical attention and ascertainment. Presenting history. Medication on admission. Diagnosis and subsequent management.

Recurrent event data collection form (page 2)

Cardiac procedure	1 = yes, 2 = no	No. of events	Date of event	Comments
Angiogram				
Angioplasty				
Stent				
CABG				
Carotid procedure				
Carotid endarterectomy				
Peripheral procedure				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				
Other procedures/ Surgery (Please specify)				
Other admission (please specify)				

Peak troponin I level ☐ ST depression ☐

ST / T wave changes ☐ TIMI – NSTEMI score ☐

NIH score ☐ TIMI – STEMI score ☐

Cause of death (if applicable) Coroner / PM ☐

I a

I b

II

Comments

Appendix 21 Pre-morbid risk factors data collection form (page 1)

Pre-morbid data **Study Number** ☐☐☐☐☐

Patient identification label **Date of Notification Event**

☐ ☐

Type

☐

GP Details

Beaumont street	01	East Oxford	03	Berinsfield	04	☐
Malthouse	05	Kidlington	06	Wantage	07	
Marcham Rd	08	Stert street	09	Other	10	

Body size

Most recent:	Height ☐	Weight ☐	BMI ☐	Date ☐
2nd most recent:	Height ☐	Weight ☐	BMI ☐	Date ☐
2nd Most recent:	Height ☐	Weight ☐	BMI ☐	Date ☐
Highest in 10yrs:	Height ☐	Weight ☐	BMI ☐	Date ☐

Blood Pressure Date of diagnosis ☐ **Drugs** ☐

On treatment for BP Y/N ☐ **Ambulatory recording ever Y/N** ☐

Most recent BP ☐ Date ☐

2nd Most recent BP ☐ Date ☐

3rd most recent BP ☐ Date ☐

Measurements (up to five) in:

2002						1995					
2001						1994					
2000						1993					
1999						1992					
1998						1991					
1997						1990					
1996											

Appendix 21 Pre-morbid risk factors data collection form (page 2)

Blood Pressure

Highest measurement prior to 1990 ☐ Date ☐

First ever recording: ☐ Date ☐

Cholesterol Date of diagnosis ☐ Drugs ☐

On treatment for high cholesterol Y/N ☐

If yes: Date treatment initiated ☐

Pre-treatment: Cholesterol ☐ LDL cholesterol ☐

Date ☐ HDL cholesterol ☐ TGs ☐

Most recent: Cholesterol ☐ LDL cholesterol ☐

Date ☐ HDL cholesterol ☐ TGs ☐

If no:

First measured: Cholesterol ☐ LDL cholesterol ☐

Date ☐ HDL cholesterol ☐ TGs ☐

Most recent: Cholesterol ☐ LDL cholesterol ☐

Date ☐ HDL cholesterol ☐ TGs ☐

Smoking (current / ex) ☐ Diabetes (NIDDM / IDDM) ☐

Previous TIA ☐ Previous CVA ☐

Angina ☐ ACS/ MI ☐

Atrial fibrillation ☐ PVD ☐

Prior aspirin / warfarin / dipyridamole ☐

Any other relevant information

☐

Appendix 22 Informant Questionnaire on Cognitive Decline

1. Remembering things about family and friends eg. occupations, birthdays, addresses	Much improved	A bit improved	Not much change	A bit worse	Much worse
2. Remembering things that have happened recently	Much improved	A bit improved	Not much change	A bit worse	Much worse
3. Recalling conversations a few days later	Much improved	A bit improved	Not much change	A bit worse	Much worse
4. Remembering his/her address and telephone number	Much improved	A bit improved	Not much change	A bit worse	Much worse
5. Remembering what day and and month it is	Much improved	A bit improved	Not much change	A bit worse	Much worse
6. Remembering where things are usually kept	Much improved	A bit improved	Not much change	A bit worse	Much worse
7. Remembering where to find things which have been put in a different place from usual	Much improved	A bit improved	Not much change	A bit worse	Much worse
8. Knowing how to work familiar machines around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
9. Learning to use a new gadget or machine around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
10. Learning new things in general	Much improved	A bit improved	Not much change	A bit worse	Much worse
11. Following a story in a book or on TV	Much improved	A bit improved	Not much change	A bit worse	Much worse
12. Making decisions on everyday matters	Much improved	A bit improved	Not much change	A bit worse	Much worse
13. Handling money for shopping	Much improved	A bit improved	Not much change	A bit worse	Much worse
14. Handling financial matters eg. the pension, dealing with the bank	Much improved	A bit improved	Not much change	A bit worse	Much worse
15. Handling other everyday arithmetic problems eg. knowing how long between visits from family or friends	Much improved	A bit improved	Not much change	A bit worse	Much worse
16. Using his/her intelligence to understand what's going on and to reason things through	Much improved	A bit improved	Not much change	A bit worse	Much worse